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LIFE PROCESSES IN GRAY NORWAY RATS DURING FOURTEEN YEARS IN CAPTIVITY

HELEN DEAN KING
The Wistar Institute of Anatomy and Biology

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HELEN DEAN KING
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THIRTEEN TEXT FIGURES AND TWO PLATES (THIRTEEN FIGURES)

THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY
Philadelphia
1939

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INTRODUCTION

Since 1919 a strain of wild gray rats (Rattus norvegicus) has been maintained at The Wistar Institute for the purpose of determining the changes that occur in these animals when bred in captivity for a number of generations. My colleague, the late Dr. Henry H. Donaldson, was cooperating in this investigation and tracing alterations in the body and organs, while I was studying changes in various life processes. A report on this work, dealing with data for the first ten generations born in captivity, was published some years ago (King and Donaldson, '29).

At the twenty-fifth generation the detailed study of rats in each succeeding generation was discontinued, and subsequently only individuals in every fifth generation were under observation. This generation, therefore, ends the period of captivity to be covered by a second report on this strain. Data for life processes in the eleventh to the twenty-fifth generation are given in this paper. Doctor Donaldson's records for organ changes in these generations will be published later.

Throughout the course of this investigation the housing conditions, care of animals, and methods of obtaining and recording data were not changed. Although food constituents varied somewhat at times, the rats always received a cooked ration, supplemented twice each week by raw vegetables and fruit. No attempts were ever made to stimulate growth and reproduction by the use of hormone extracts or special diets, nor were any individuals treated with x-rays, radium or other agencies in an endeavor to induce mutations. Thus the strain was maintained constantly under fairly uniform environmental and nutritive conditions that furnished adequate food, security from enemies, and protection from extreme temperatures.

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In this investigation, as in others continued over a long period, contingencies have arisen at times that had a marked effect on animals then under observation. Unfavorable conditions in the colony decreased fertility and the growth rate of individuals in the eleventh to the fifteenth generation. Similar effects followed removal of the colony to temporary quarters in 1932, and its subsequent transfer to a new location the following year.

Various subjects are discussed here in the same order as in the previous report, and a new section has been added dealing with the mutations that appeared in later generations. Many tables contain a summary of relevant data for the first ten generations in order to show successive steps in the series of changes that occurred in these rats during 14 years of captivity (1919–1933).

GROWTH IN BODY WEIGHT

Changes in the weight of the body with age were determined for 1674 individuals from the fifteen generations covered by this report, approximately the same number of rats being taken from each generation. To facilitate an analysis of the findings, data for five successive generations were combined into the three groups given in reference tables 1 to 3.

The body weight relations of the sexes during early postnatal life warrant consideration in view of the fact that in the first generation the average body weight of females exceeded that of males at 13 and at 30 days of age (King, '23), but in the second to the tenth generations weights of males exceeded those of females at all age periods (King and Donaldson, '29). A weight excess in young females, although similar to Donaldson's ('06) finding for young albino rats, does not accord with other determinations of the weight relations of the sexes in albinos (Jackson, '13; King, '15; Donaldson, '24).

When the first report on this strain was written sufficient data on the birth weights of gray rats had not been obtained to furnish the norms that are necessary in order to determine the relative growth rate of the sexes during the suckling period. Such data are now available, since a recent paper (King, '35) gives birth weights for 6295 gray rats taken mainly from later generations. These records give the average weight of 3228 males as 5.5 gm., and that of 3067 females as 5.2 gm. (King, '35). Thus at birth the body weight of gray males exceeds that of females by 0.3 gm. (5.5 per cent).

TABLE 1

Increase in the weight of the body with age for individuals in the eleventh to the fifteenth generation of captive gray rats

AGE IN DAYS	MALES				FEMALES			
	Number of individuals	Body weight in grams			Number of individuals	Body weight in grams		
		Average	Highest	Lowest		Average	Highest	Lowest
13	269	18	25	14	278	17	23	13
30	269	44	78	28	278	42	75	26
60	269	89	149	49	278	80	142	47
90	269	136	247	83	276	114	184	74
120	269	168	290	96	269	144	208	90
151	267	199	308	127	260	168	253	105
182	265	225	343	141	259	185	271	115
212	263	244	358	152	258	197	277	129
243	262	263	395	162	265	208	306	145
273	257	276	433	171	258	219	340	152
304	254	291	452	209	263	229	344	164
334	254	302	441	186	265	238	355	172
365	253	310	471	220	250	246	330	178
395	250	322	464	236	251	254	343	183
425	249	333	490	245	251	260	387	190
455	242	336	479	250	245	268	391	189
486	239	348	490	252	231	277	415	186
516	234	357	502	269	226	288	433	182
547	224	365	497	282	228	292	417	197
578	214	375	547	265	217	298	398	220
608	209	379	553	289	203	302	404	219

Taking these weights as norms, it is shown by data in table 1 that in the eleventh to the fifteenth generations the sexes were growing at approximately the same rate when 13 days of age. At 30 days, however, the weight difference of 2 gm. (4.5 per cent) indicates that females were then growing more rapidly than males. In later generations (tables 2 and 3) the growth rate of females exceeded that of males throughout the suckling period, since at 13 days the average weights of males and females were the same, and at 30 days the weight excess of males was but 2 per cent. Subsequently the growth rate in females decreased while that in males increased. The weight excess of males had increased to about 21 per cent by the time the rats were 8 months old. Thereafter the average weight differences between the sexes remained fairly constant. It thus appears that in gray rats, as in albinos (Donaldson, '06), the growth curves are similar to those for man in that, although males tend to be heavier than females at birth and

TABLE 2

Increase in the weight of the body with age for individuals in the sixteenth to the twentieth generation of captive gray rats

AGE IN DAYS	MALES				FEMALES			
	Number of individuals	Body weight in grams			Number of individuals	Body weight in grams		
		Average	Highest	Lowest		Average	Highest	Lowest
13	283	19	29	14	275	19	27	13
30	283	50	79	34	275	49	69	34
60	283	110	198	51	275	97	170	53
90	283	166	260	85	273	139	212	68
120	283	212	302	97	254	172	252	86
151	281	253	354	121	255	201	270	112
182	280	279	401	136	253	219	297	123
212	277	302	420	146	254	234	307	132
243	275	318	422	184	244	247	336	162
273	275	331	452	203	245	258	353	182
304	273	343	465	225	248	268	344	175
334	270	355	472	254	255	278	363	198
365	269	366	498	286	254	288	378	210
395	268	376	504	284	251	295	403	210
425	264	384	512	290	247	301	403	198
455	261	396	527	302	247	309	402	204
486	259	404	547	287	244	314	402	240
516	253	412	567	326	229	323	426	243
547	243	423	549	338	225	329	429	240
578	237	434	560	333	217	338	438	252
608	231	439	572	353	215	344	462	256

during adult life, females grow at a more rapid rate during early life. An acceleration in the growth rate of young females has been noted also in the guinea pig (Bessesen and Carlson, '23), in the mouse (Gates, '25) and in the cat (Latimer and Ibsen, '32), as well as in man (Baldwin, '14; Davenport, '26; Appleton, '28).

TABLE 3

Increase in the weight of the body with age for individuals in the twenty-first to the twenty-fifth generation of captive gray rats

AGE IN DAYS	MALES				FEMALES			
	Number of individuals	Body weight in grams			Number of individuals	Body weight in grams		
		Average	Highest	Lowest		Average	Highest	Lowest
13	280	18	28	14	289	18	25	15
30	280	48	89	35	289	47	78	34
60	280	109	180	53	289	91	160	58
90	280	174	276	94	284	147	216	83
120	280	216	309	137	265	183	253	110
151	279	249	354	179	269	208	286	129
182	279	275	385	188	273	225	305	137
212	279	297	400	203	276	239	335	144
243	279	314	442	239	273	252	345	164
273	278	327	445	251	271	264	352	175
304	276	341	446	264	276	276	368	186
334	274	352	445	262	260	282	387	203
365	272	369	458	304	266	289	368	203
395	272	372	482	298	257	295	387	212
425	267	382	515	305	260	299	382	230
455	263	396	518	312	256	306	388	245
486	257	400	524	303	252	310	405	251
516	249	412	554	347	252	321	416	246
547	247	423	550	353	247	329	418	277
578	234	424	551	356	240	338	440	283
608	225	441	553	364	227	342	447	285

Graphs in figure 1, constructed from data in tables 1 to 3, indicate the changes in body weight with age in successive generation groups of male rats and form a better basis for discussion than do the data in tables 1 to 3.

All graphs in figure 1 have approximately the same form, but graph 1 runs at a relatively low level due, in part, to the

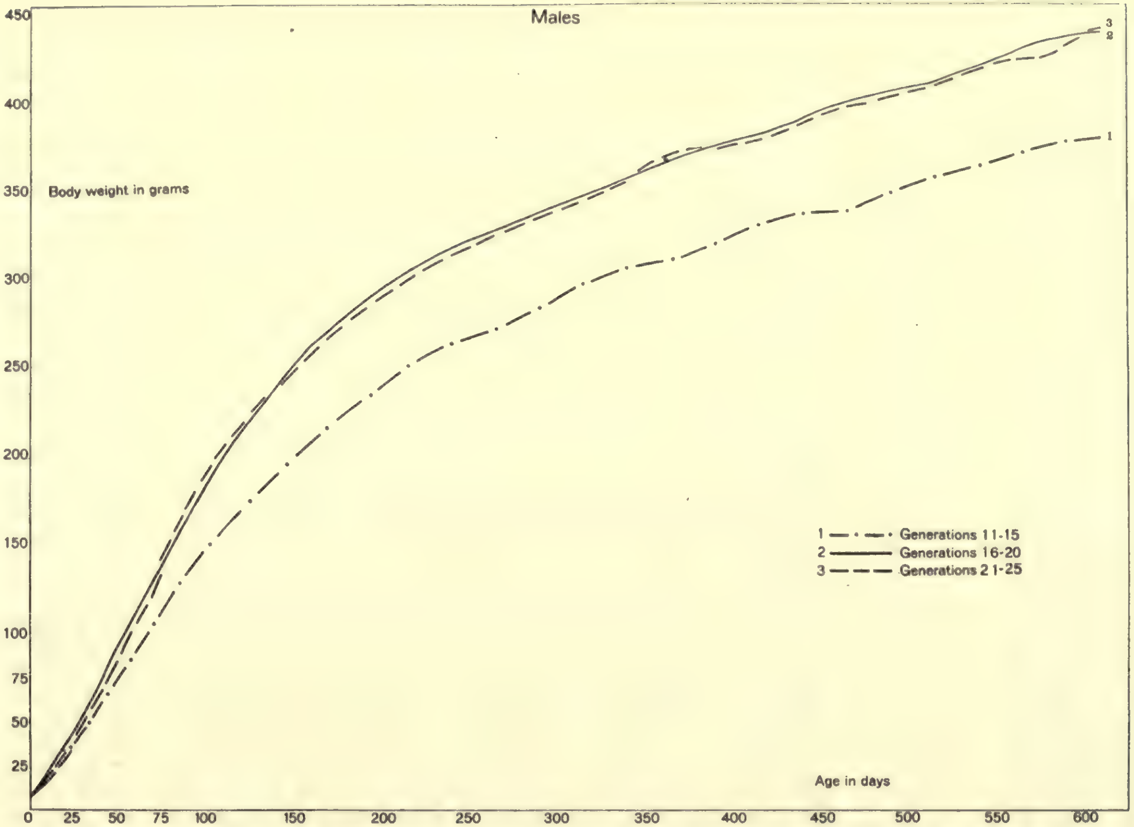

Fig. 1 Changes in the weight of the body with age in three generation groups of males.

fact that in individuals of this group growth was retarded by adverse conditions in the colony. That improved environmental and nutritive conditions had a favorable influence on body growth is shown by the rapid rise of graphs 2 and 3, which run very close together during their entire length. The difference in the level of the graphs during the latter part of their course indicates that adult males of the last two generation groups weighed about 15 per cent more than did those of the first group. The temporary check to body growth resulting from the transfer of the colony to a new location accounts for the depression near the end of graph 3.

Body weight changes with age in the three groups of females (tables 1 to 3) are shown graphically in figure 2.

While the graphs in figure 2 are similar in form to those in figure 1, they run at lower levels, as females tend to weigh less than males at all age periods after weaning.

Females of the last two generation groups responded to better environmental conditions by growing at a more rapid rate during early life, and attaining a larger size than did females of earlier generations. They weighed, on the average, about 13 per cent more during adult life than did females of the first group, as the levels of the graphs in figure 2 indicate.

According to Sorin ('32), litter size has a marked effect on the body growth of guinea pigs. This factor could not have influenced growth in gray rats, since throughout this investigation the great majority of litters used for study contained either five or six individuals: no litters of less than four or more than seven young were ever reared.

After twenty-five generations had been born in captivity, both rate and extent of body growth in males had increased greatly, as shown by the graphs in figure 3, which were constructed from body weight data given in table 5.

In figure 3 graph (A) rises gradually from the beginning to the end of its course, and shows no evidence of any pronounced growth acceleration during the adolescent period in males of the first generation. Body weight increase during later life was very uniform, and at the final weighing these

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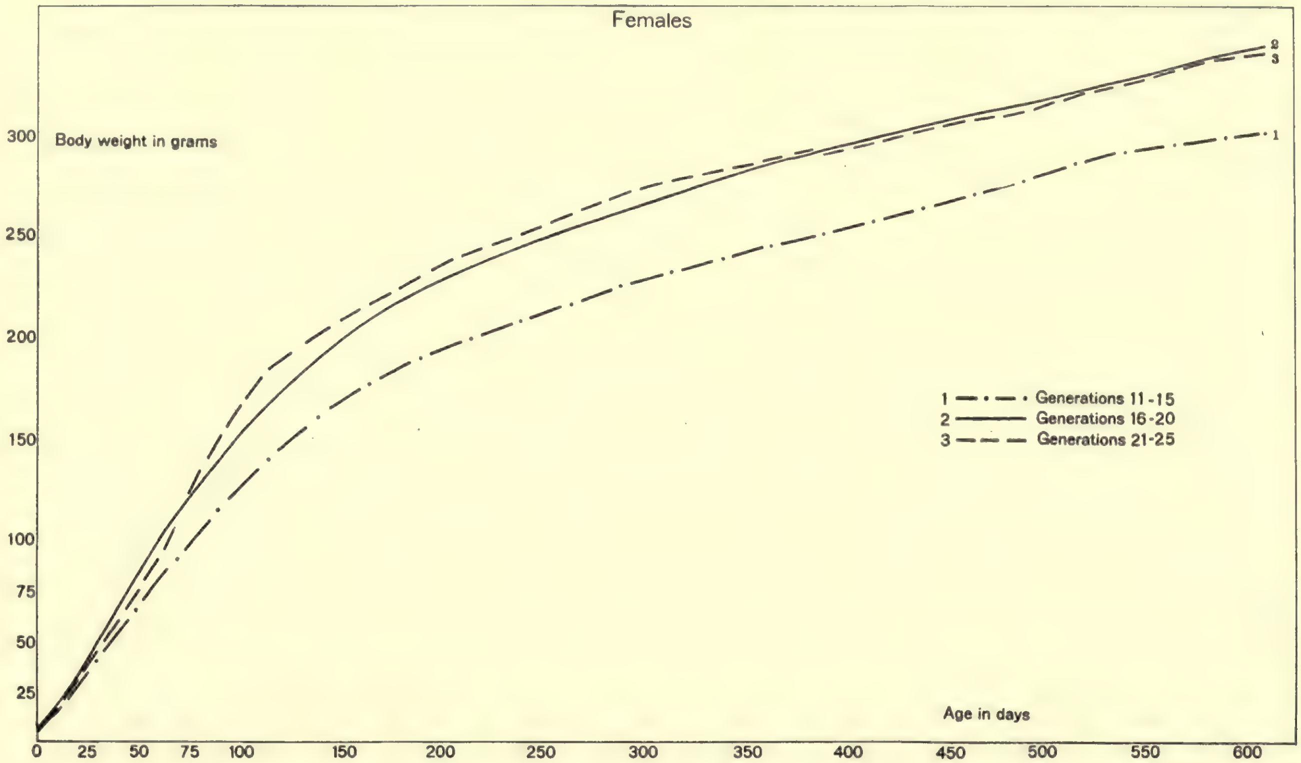

Fig. 2 Changes in the weight of the body with age in three generation groups of females.

males attained an average weight of 362 gm. Graph B, for males of the twenty-fifth generation, rises rapidly and does not tend to flatten until the age period of about 150 days, thus indicating a marked growth acceleration during adolescence and early maturity. The variance in the levels of graphs A and B during the period of 60 to 150 days indicates a weight difference between these two groups of males of some 35 per cent. At subsequent age periods the graphs run nearly parallel, but at levels indicating that males of the last generation were about 20 per cent heavier than those of the first generation during the greater part of adult life, and 17 per cent heavier at the final weighing when their average weight was 440 gm.

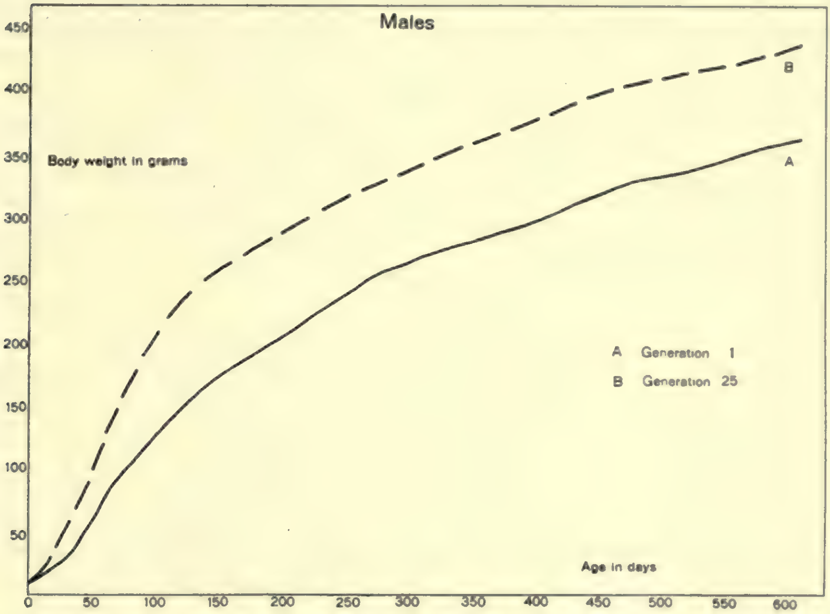

Fig. 3 Body growth in males of the first and of the twenty-fifth generation.

Data from table 6 were used in constructing the growth graphs for females of the first and of the twenty-fifth generation, which are shown in figure 4.

The graphs in figure 4 run more irregularly than do those in figure 3, because the effects of early pregnancy and of lactation on body weights could not be eliminated nor offset in compiling the data. The course of these graphs indicates that females of the twenty-fifth generation grew much more rapidly during early life, and were heavier at all subsequent age periods, then females of the first generation, their weight excess at the end of the weighing period being about 19 per cent.

At the twenty-fifth generation, both sexes of gray rats were growing during adolescence and early maturity at a rate approaching that characteristic of albino rats maintained in captivity for a long period of time. The average body weights of adult grays, however, were greater than those of albinos of like ages. The effects of captivity on the rate and extent of body growth in gray Norway rats are similar to those that have occurred in various domesticated mammals, such as cattle, horses, and sheep. These animals, as Darwin (1875) has shown, grow more rapidly and attain a much larger size than did their wild prototypes. This growth increase in domesticated animals is due, in all probability, to selective breeding and to the more favorable conditions of environment and of nutrition that captivity entails.

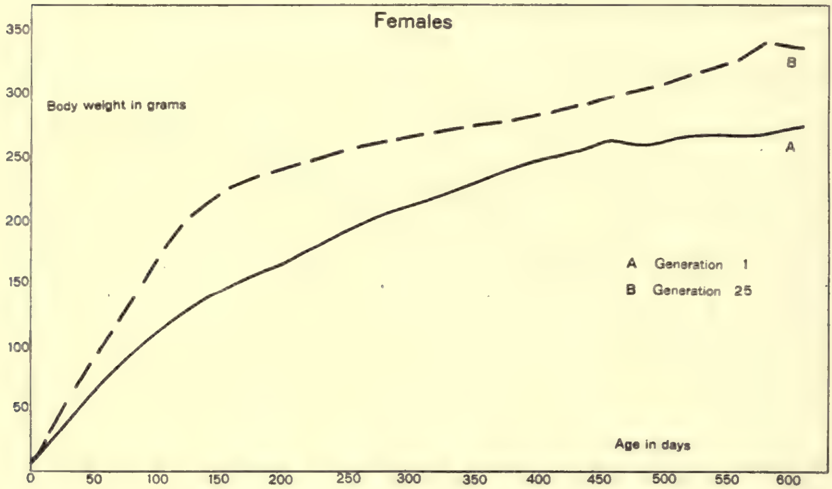

Fig. 4 Body weight in females of the first and of the twenty-fifth generation.

Important experimental work during recent years has shown that body growth in rats can be accelerated, and also greatly increased, by feeding nutritional diets or by the use of growth promoting hormones (Robertson, '16 a; Evans, '24; Osborne and Mendel, '26; Mendel and Cannon, '27; Smith and Bing, '28; Anderson and Smith, '32; Mendel and Hubbell, '35, etc.). To what extent other life processes are affected by these agencies has received little attention, as yet. Whether rapid growth during early life is beneficial to the individual and tends to a more active reproductive life and to longevity has long been questioned. Precocious body growth in man has never been deemed advantageous, since it seems to render individuals prone to certain diseases and to shorten the life span. It has been suggested that the difference in the growth rate of the sexes may be responsible for the fact that women tend to live longer than men, even when the latter have not been engaged in hazardous occupations that are liable to shorten life.

The relation between growth rate and longevity in albino rats has been investigated by McCay and his associates (McCay, '33; McCay and Crowell, '34; McCay, Crowell and Maynard, '35). These investigators found that individuals in which growth was retarded for a number of months by restricting the diet still retained the power to grow when they were old if then they were given adequate food. They did not, however, attain the size of animals that had grown rapidly during early life. Individuals with a retarded growth rate lived longer than did the controls, and females had a longer life span than males. McCay ('33) states: "No one has ever found it possible, however, to have both rapid growth with early attainment of maturity and longevity: It is possible that longevity and rapid growth are incompatible and that the best chance for an abnormally long life span belongs to the animal that has grown slowly and attained a late maturity."

The greater growth acceleration during early life and larger adult size of gray rats in later generations had no apparent detrimental effects on other life processes. On the contrary, as shown by data in various tables, these rats attained maturity earlier than did those of preceding generations, their fertility was greater, the reproductive period longer, mortality during early life much less, and the average life span prolonged. There is no evidence, however, to warrant an assumption that rate and extent of body growth in these rats were precocious. Possibly growth was approaching the optimum for the race when individuals are maintained under environmental and nutritive conditions favorable for the full expression of growth activators without overstimulating them.

Although intrauterine factors doubtless play a major role in determining the growth of fetal young, rate and extent of postnatal growth, if environmental and nutritive conditions are uniform, must depend mainly upon growth potentialities which have their basis in the genetic constitution of the individual. It has been shown for the guinea pig (Bessesen and Carlson, '23), the rabbit (Kopéc, '26), the mouse (Kopéc, '29) and the rat (Dunn, '08; King, '16) that the early postnatal growth of individuals of the same litter is usually in the order of their birth weights. Individuals that are large at birth tend to grow more rapidly and to attain a larger size when adult than do those with a low birth weight.

Rats much below normal weight at birth, so-called runts, never attain the body size of other members of the litter even when reared under nutritive conditions that normally induce rapid growth (King, '16). Runts, apparently, are individuals in which growth processes have been retarded by some inherent factor. Their inability to grow at a normal rate cannot be due merely to nutritional handicaps during fetal life, since restriction of growth by malnutrition does not deprive normal rats of the power to grow when the diet is again adequate, as McCay, Crowell and Maynard ('35) have shown.

Another type of individual in which body size during adult life is as much above the norm as that of the runt is below it has been found in this strain of captive gray rats. Such rats are not noticeably large at birth, and they grow during early life at about the same rate as other individuals of the same sex in the litter. To show the course of body growth in these individuals, growth data were compiled for twenty selected pairs of rats of each sex belonging in the sixteenth to the twenty-fifth generations. Each pair of rats of the same sex, one large and one small, were members of the same litter. All were individuals that continued to increase in weight throughout adult life, and were apparently in good physical condition at the end of the weighing period. Differences in their body weights, therefore, cannot be attributed to disease. The smaller individuals of the pairs were not runts, nor was their growth restricted, as is shown by the fact that their average body weights at any age period were not significantly lower than corresponding weights for all rats in the generation groups from which they came (tables 2 and 3). Body weight increase with age in these rats is given in table 4.

TABLE 4

Increase in body weight with age for twenty pairs of males and of females from the sixteenth to the twenty-fifth generation of captive gray rats. Each pair of the same sex (one large and one small) from the same litter

AGE IN DAYS	MALES		FEMALES	
	Average body weight in grams		Average body weight in grams	
	Large	Small	Large	Small
30	52.2	51.1	47.6	47.2
60	113.7	106.7	104.4	103.6
90	187.9	176.1	155.4	147.8
120	229.9	214.9	187.5	183.1
151	264.4	254.8	209.5	208.8
182	286.9	272.8	229.6	224.9
212	305.1	294.5	247.0	239.9
243	314.7	306.3	258.8	252.8
273	330.8	318.5	277.2	261.0
304	342.2	327.3	287.2	269.0
334	363.7	340.9	307.3	281.4
365	378.8	354.2	308.6	287.8
395	404.0	366.1	330.0	294.9
425	427.9	377.6	333.3	298.8
456	444.8	390.7	337.6	311.3
486	465.3	401.2	357.1	312.3
516	488.2	412.8	365.5	321.2
547	502.2	427.1	380.3	325.5
578	517.8	431.3	400.0	328.8
608	528.1	431.8	418.1	332.9

The data in table 4 are shown graphically in figure 5.

In figure 5 the graphs for males (1 and 2) run parallel and at nearly the same level until the age period of about 300 days. Up to this point the space between the graphs represents a weight difference in the two groups of approximately 4.5 per cent, the weights of the smaller individuals being taken as the standards in computation. Subsequently the two graphs diverge sharply; graph 1 mounts upward rapidly, graph 2 rises at a slower rate. At the 400-day period the larger males had increased their weight excess to 10 per cent, and they were 22.3 per cent heavier at the end of the weighing period.

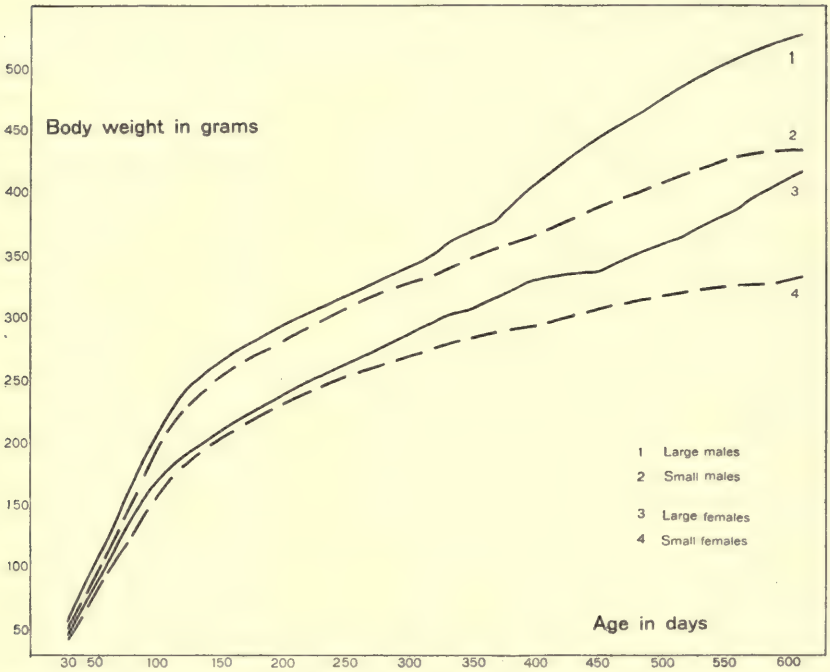

Fig. 5 Body growth in pairs of large and small individuals from the same litter.

Growth graphs for the two groups of females (3 and 4) run much the same as those for males, although they begin to diverge at an earlier age period. At 212 days the space between the graphs represents a weight difference between the two groups of about 3 per cent. At 300 days this difference has more than doubled. The weight excess of the larger females was 11.9 per cent at 400 days and had become 25.6 per cent at the last weighing.

Autopsies made on a number of these large and small individuals disclosed no conditions that would account for the difference in their size. In the large individuals the body had increased as a whole and there was no evidence of differential growth in any of the organs.

As the number of these exceptional individuals increased as the generations advanced, it seems probable that the condition is inherited, and that these rats contained some genetic factor, or factors, that acted mainly during adult life to supplement the action of growth activating agencies. Genetic factors are known to play an important role in inciting and regulating growth processes, and their action is probably physiological, since there is no evidence, as yet, of the existence of specific size genes in mammals. Green ('31, '33) found that genes producing brown and dilute color in mice also increase the body size of the individuals. In confirming Green's finding, Castle, Gates and Reed ('36) have given evidence indicating that these genes influence body size "by virtue of their own physiological action."

Some of these large individuals became exceedingly savage and often severely injured or killed other inmates of the cage. Males with this 'killer' trait did not molest females of any age, but attacked adult males smaller than themselves and young males approaching maturity. Vicious females usually harmed only weaker individuals of their own sex. The 'killer' trait in these rats was doubtless a heritage from their wild ancestry, associated with the polygamous condition common to many animals living in their natural habitat.

Individuals much larger than their litter mates of the same sex have appeared occasionally in all strains of rats that have been under investigation in the colony during the past 20 years. 'Killers' have been found, however, only in captive grays and in mutant strains, particularly in mutant albinos.

VARIABILITY IN BODY WEIGHT

Body-weight variability in both sexes of gray rats changed considerably as the generations advanced. To indicate the trend and extent of this change, coefficients of variation for body weights at different age periods in individuals of three generations are given in tables 5 and 6. In these tables the series of coefficients for the first generation are reproduced from the former report on this strain (King and Donaldson, '29). Coefficients for the age period of 13 days were calculated from the average weights of males and females in each litter, as were also those for the 30-day period in the first generation. For all other age periods, the coefficients were calculated from individual data.

Coefficient of variation for body weights of males are given in table 5, those for females in table 6.

Tables 5 and 6 are given for reference only, since a graphic representation of the data for the first and for the twenty-fifth generations (fig. 6) shows more clearly the marked changes that occurred in the body-weight variability of gray rats during the period of captivity covered by the present report.

In figure 6 graphs (A and C) for body-weight variability in the two generation groups of males have the same general trend in that each rises to a maximum at an early age period, and then declines. Graph C, however, is much below graph A at all points, and its level as age advanced indicates that body-weight variability in males of the twenty-fifth generation was less than half of that in males of the first generation during the major portion of adult life, and even lower near the end of the weighing period when senility was beginning.

Graphs B and D, depicting body-weight variability in females of the two generation groups, run more irregularly than do those for males, because maximum variability in females of the first generation did not come until the rats were 13 months of age. For age periods up to 4 months differences between the graphs are not statistically important, but subsequently the levels of these graphs indicate that body-weight

TABLE 5

Coefficients of variation for body weights in three generations of captive gray males

AGE IN DAYS	FIRST GENERATION			TWENTIETH GENERATION			TWENTY-FIFTH GENERATION		
	Number of individuals	Average body weight in grams	Coefficients of variation	Number of individuals	Average body weight in grams	Coefficients of variation	Number of individuals	Average body weight in grams	Coefficients of variation
13	51	15	12.2±0.82	56	19	15.9±1.01	50	18	6.3±0.43
30	51	33	13.0±0.86	56	50	12.3±0.78	50	56	17.1±1.15
60	51	82	24.1±1.60	56	114	15.5±0.99	50	124	17.7±1.13
90	51	116	26.2±1.74	56	168	17.4±1.11	50	188	20.3±1.37
120	51	149	28.2±1.88	56	223	16.9±1.08	50	231	14.8±0.99
151	51	176	24.2±1.61	56	260	16.8±1.08	50	256	13.0±0.88
182	51	196	23.4±1.55	55	288	15.9±1.02	50	274	11.6±0.78
212	51	218	21.8±1.45	55	309	14.5±0.93	50	293	9.9±0.66
243	50	235	23.7±1.60	55	330	13.3±0.85	50	312	8.8±0.60
273	50	254	22.4±1.50	55	342	12.8±0.82	50	325	8.3±0.56
304	50	266	21.5±1.45	55	362	11.9±0.77	50	340	8.1±0.55
334	50	277	19.8±1.33	55	372	10.8±0.69	50	353	8.0±0.54
365	48	287	19.5±1.33	55	386	10.1±0.65	50	364	7.3±0.49
395	48	297	19.5±1.34	55	399	9.6±0.62	50	377	6.3±0.43
425	47	312	17.6±1.22	52	404	9.7±0.64	50	390	5.4±0.37
455	47	322	19.2±1.32	51	407	8.5±0.56	49	401	5.1±0.35
486	46	332	17.3±1.21	51	412	8.8±0.59	49	407	4.5±0.30
516	43	335	17.4±1.26	49	417	9.9±0.78	47	413	4.1±0.28
547	41	346	16.7±1.24	47	425	9.3±0.65	46	420	3.7±0.26
578	39	358	18.3±1.39	46	436	9.2±0.64	45	428	3.6±0.25
608	38	362	17.1±1.32	46	432	9.1±0.64	43	438	5.7±0.42

TABLE 6

Coefficients of variation for body weights in three generations of captive gray females

AGE IN DAYS	FIRST GENERATION			TWENTIETH GENERATION			TWENTY-FIFTH GENERATION		
	Number of individuals	Average body weight in grams	Coefficients of variation	Number of individuals	Average body weight in grams	Coefficients of variation	Number of individuals	Average body weight in grams	Coefficients of variation
13	59	16	14.6±0.90	53	19	15.8±1.03	51	18	5.5±0.37
30	59	37	17.3±1.07	53	49	14.7±0.96	51	52	16.3±1.09
60	59	75	19.8±1.22	53	97	16.9±1.10	51	109	17.5±1.17
90	59	101	16.9±1.04	52	138	17.9±1.18	50	158	12.9±0.87
120	59	123	16.0±0.99	48	179	13.8±0.95	47	195	13.5±0.88
151	56	142	16.6±1.03	50	206	12.2±0.82	50	218	11.9±0.80
182	54	154	17.8±1.13	48	225	11.8±0.81	47	232	11.8±0.82
212	50	172	17.9±1.20	49	243	10.6±0.72	49	241	10.9±0.68
243	52	189	18.2±1.26	45	257	11.7±0.83	49	250	10.2±0.86
273	51	204	19.1±1.27	49	265	10.1±0.81	46	261	9.8±0.69
304	47	210	19.9±1.38	46	278	10.0±0.70	49	265	8.4±0.57
334	49	222	20.6±1.40	49	288	8.5±0.58	47	270	8.1±0.56
365	47	233	20.4±1.41	50	301	9.1±0.61	49	277	7.5±0.51
395	47	242	22.3±1.54	46	307	9.3±0.65	46	283	6.7±0.47
425	43	248	21.1±1.47	48	315	9.1±0.63	48	289	6.9±0.48
455	44	261	18.9±1.35	47	319	8.7±0.60	47	297	6.5±0.46
486	43	258	19.5±1.41	46	324	8.7±0.61	48	302	6.1±0.42
516	37	264	18.3±1.43	44	328	9.1±0.65	42	317	6.7±0.49
547	36	262	19.4±1.54	44	337	9.9±0.71	42	322	6.4±0.47
578	34	267	16.4±1.34	42	343	9.2±0.68	44	340	7.5±0.54
608	31	272	15.3±1.28	39	344	11.3±0.86	43	337	7.7±0.56

variability in females of the twenty-fifth generation was significantly less than that in females of the first generation.

A correlation between body-weight variability and the growth rate in both sexes of gray rats is indicated by the fact that in all generation groups of males (table 5) and in the last two generation groups of females (table 6) variability was at its maximum when the rats were young and growing rapidly, and then decreased as the growth rate declined during adult life. A similar correlation has been found in the albino rat (King, '15), in the mouse (Robertson, '16; Saller, '27; Kopéc, '32), as well as in man (Boas and Wissler, '05).

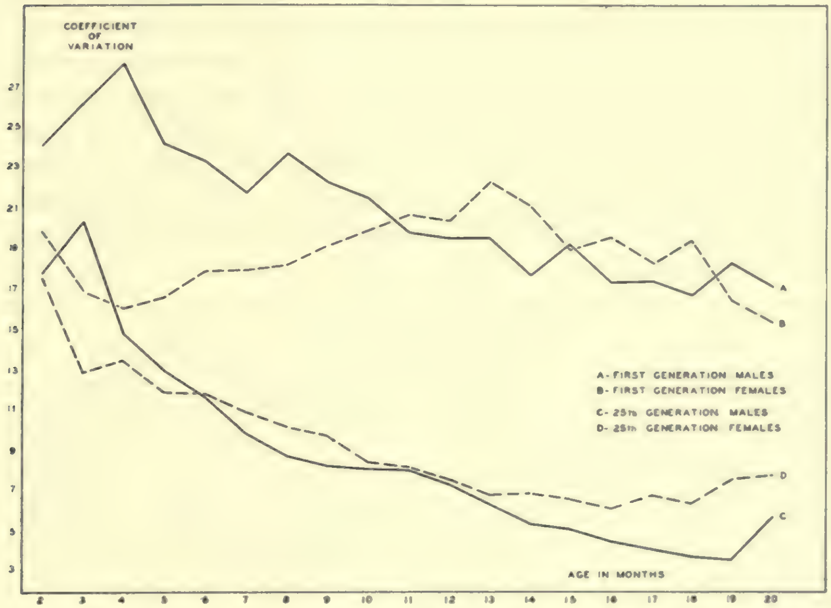

Fig. 6 Body-weight variability with age in the first and in the twenty-fifth generation.

There is no sex difference in body-weight variability at birth in gray rats. Coefficients of variation, calculated from a large series of birth weights (King, '35) give for males a value of 13.7 ± 0.11, and for females 13.6 ± 0.12. Comparison of corresponding coefficients in tables 5 and 6 and the graphs in figure 6 show, however, that males tended to be more variable than females during early postnatal life, and less variable during later life. It seems probable that the greater body-weight variability of gray females during adult life can be ascribed to reproductive activity, as Kopéc ('32) has suggested is the case in mice. Pregnancy and lactation have marked effects on the body weights of breeding females. When weight determinations are made at stated intervals over a considerable period of time, the data obtained often include weights for lactating females and for those in early stages of pregnancy, even though, as in this investigation, weighings are omitted when females are known to be pregnant or when their weights are greatly reduced because they are suckling large litters. Coefficients of variation for body weights of adult females, calculated from data thus obtained, are undoubtedly larger than would be a series of coefficients based on data for unmated females whose weights had not been affected by reproductive processes. Taking this fact into consideration, the greater body-weight variability of females during adult life has no significance. For age periods during early life, where the two series of data are strictly comparable, body-weight variability in males was somewhat greater than that in females. A similar sex relation in body-weight variability has been found in albino rats (Jackson, '13; King, '18, '19) and in mice (Robertson, '16; Saller, '27; Kopéc, '32). These findings accord with the view that throughout the organic world males, in general, tend to be more variable than females.

Darwin (1875) was of the opinion that variability of every kind is caused directly or indirectly by changed conditions of life, and that, "if it were possible to expose all individuals of a species during many generations to absolutely uniform conditions of life there would be no variability." In light of our present knowledge of genetics, it is probable that changed conditions of life in captivity had little effect on the body-weight variability of gray rats. The gradual decrease in the variability of these rats as the generations advance can doubtless be ascribed mainly to the method used in selecting individuals to propagate the race and to inbreeding.

All individuals in this strain of rats descended from six pairs of wild rats. No new stock has ever been added. Except in the descendants of one pair of feral animals, few matings were made in early generations between individuals that were very closely related. Rigid selection of only the most vigorous animals as parents of the succeeding generations gradually eliminated descendants of some of the wild rats, thus rendering the stock more homogeneous. For reasons given in the final section, all individuals in the twenty-first to the twenty-fifth generations were inbred, brother and sister. This close inbreeding undoubtedly tended to reduce variability and so is responsible, in great measure, for the low body-weight variability in rats of the twenty-fifth generation.

THE REPRODUCTIVE PERIOD

When wild animals are brought into captivity, the most marked effect of the changed conditions of life, at first, is on their reproductive activity. Some wild forms never breed after being removed from their natural habitat; others produce but a small number of young which often must be reared by foster mothers since their own mothers do not care for them. In most cases a considerable period of time elapses before individuals become sufficiently adjusted to their new environment to produce and rear strong, vigorous offspring. The cause of this low fertility in wild animals when first captured is unknown, and, as Darwin (1875) has stated, "we can only infer that it is caused by a change of some kind in the natural conditions of life."

Thirty-six wild rats (sixteen males and twenty females) were brought to the laboratory to serve as foundation stock for this strain of captive grays. Judging from their size, the youngest of the females were at least 3 months of age when captured, the oldest being probably a year old. None of the females were pregnant when captured, although all of them were vigorous and seemingly free from disease. The changed conditions of life to which these rats were subjected affected reproductive processes adversely, causing sterility in some females and greatly reducing fertility in others. Only six of the wild females bred in captivity, and the litters they cast were small. Under their new environment wild females, with one exception, seemed incapable of suckling their offspring, and their litters were either destroyed soon after birth or neglected. In order to save the young it was necessary to remove them from the nest soon after their birth and give them to lactating albino females to rear. Restrictions to breeding resulting from change of habitat began to disappear in individuals of the second generation, and subsequently the great majority of females reared were fertile and able to rear their young.

It has been stated (Eaton and Stirrett, '28) that wild rats become sexually mature when they are about 3 months of age, but this statement lacks confirmation. In light of the breeding data obtained from trapped wild rats and from individuals in the early generations of captive grays, I am inclined to the opinion that gray females living under natural conditions do not begin to breed, as a rule, until they are at least 4 months of age.

With the advance of the generations there was a marked increase in the length of the reproductive period, as is shown by the data in table 7.

In later generations, as in the earlier ones, there was considerable variation in the time at which individual females began breeding. While some females cast their first litters when less than 3 months of age, the majority of them did not breed until they were at least 4 months old. The average age of females at the onset of breeding decreased steadily as the generations advanced, and was but 119 days at the twenty-fifth generation (table 7). Thus, at the end of the period of captivity covered by this report, the reproductive life of females began 147 days earlier than did that of females in the first generation whose average age at the inception of breeding was 266 days. Generation changes in the age of females at the beginning and at the end of reproductive life are indicated by the graphs in figure 7.

The earlier breeding of females in late generations can be ascribed, in part at least, to their more rapid growth during adolescence. As a rule, rats that grow rapidly when young are the ones that begin to breed at an early age; those that grow slowly do not mature until much later. It is possible, also, that in the rat, as in the domestic fowl (Warren, '34; Hays, '36) age at sexual maturity is an inherited character that can be influenced by selection. Assuming that some individuals in the foundation stock of this strain carried genes tending to induce early maturity, such genes would have accumulated in the stock after a time because of inbreeding. The

TABLE 7

Length of the reproductive period in the tenth to the twenty-fifth generation of captive gray rats

GENERATION OF BREEDING FEMALES	EARLIEST AGE AT WHICH A LITTER WAS CAST	LATEST AGE AT WHICH A LITTER WAS CAST	TOTAL LENGTH OF REPRODUCTIVE PERIOD	AVERAGE AGE WHEN FIRST LITTER WAS CAST	AVERAGE AGE WHEN LAST LITTER WAS CAST	AVERAGE LENGTH OF REPRODUCTIVE PERIOD
	days	*days*	*days*	*days*	*days*	*days*
10	101	692	591	207	490	283
11	93	642	549	210	509	299
12	90	730	640	175	506	331
13	108	652	544	169	510	341
14	130	784	654	209	548	339
15	99	802	703	172	521	349
16	104	728	624	195	559	364
17	78	646	568	137	522	385
18	87	665	578	151	546	395
19	75	657	582	135	547	412
20	88	655	567	136	512	376
21	95	731	636	143	535	392
22	79	655	576	124	525	401
23	84	617	533	128	522	394
24	88	643	555	140	540	400
25	76	667	591	119	559	440
10–25			593	159	528	369
1–9			517	226	453	227

majority of litters reared in later generations were cast by females that had grown rapidly and bred at an early age, but selection of litters to continue the strain was not based on the early breeding of the mothers, but on the size and vigor of the young at birth, the number of individuals in a litter, and its sex composition.

In rats maintained under laboratory conditions reproduction ends, usually, when the animals are about 18 months of age, although cases are known where young were born when females were over 2 years old. The time at which the menopause appears depends largely upon the physical status of the females, especially on their ability to resist pneumonia. This infection soon ends reproductive activity, although affected individuals may live for some months.

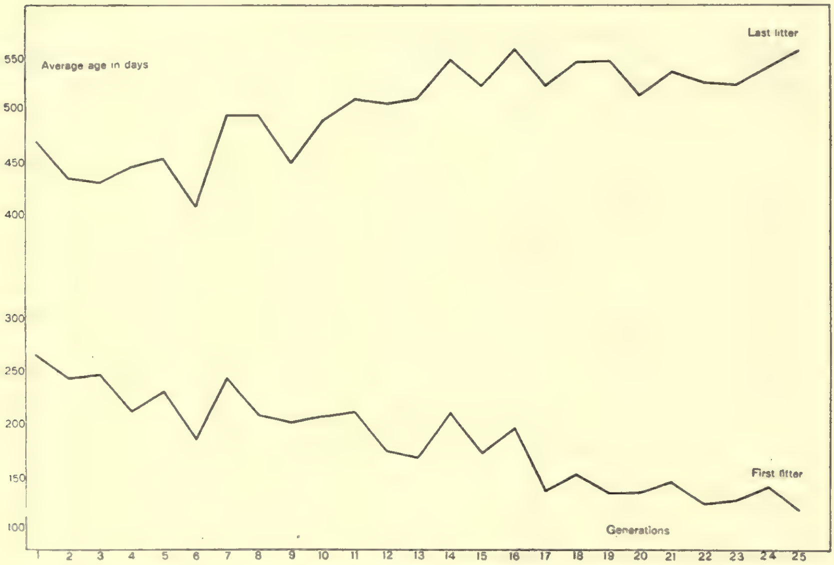

Fig. 7 Average age of females when the first and the last litters were cast.

The age at which individual females in later generations stopped breeding varied greatly, the range being 185 days (table 7). The average age of females at menopause tended to advance with the generations, as is indicated by the course of the upper graph in figure 7.

The better physical condition of the rats after they had been in captivity for several years, and the less frequent occurrence of tumors and infections of the genital tract, probably account in great measure for the extension of reproductive life. There is also a possibility that heredity may be a factor involved in defining the limits of reproductive activity, since in some cases relatively young females, seemingly in good physical condition, cast only two or three litters; in other cases all females of a given litter produced approximately the same number of litters and stopped breeding at about the same age.

Changes in the average length of the reproductive period in females of the first twenty-five generations are shown by the graph in figure 8.

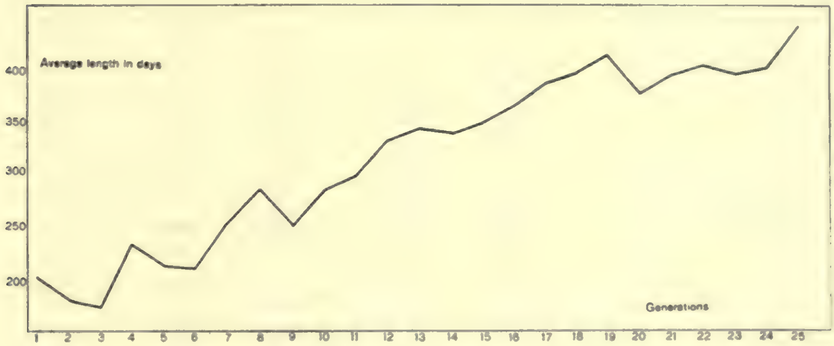

Fig. 8 Average length of the reproductive period in different generations.

Although there are irregularities at the beginning of the graph in figure 8, its general trend is upward. There are noticeable depressions at the ninth and twentieth generations, ascribable to the fact that in these generations breeding was checked because a number of females had ovarian cysts or developed pneumonia at an early age. The difference in the level of the graph at its beginning and the level at its end indicates that, at the twenty-fifth generation, the average length of the reproductive period (440 days) was more than twice that (204 days) in the first generation. This extension of reproductive life and also the increased fertility of captive gray rats, which will be shown in the following section, accord with the findings of Darwin (1875) and others that under the more favorable environmental and nutritive conditions of life in captivity domesticated animals breed earlier and longer, and are more prolific than their wild ancestors.

FERTILITY

Literature on the fertility of wild gray rats deals chiefly with records of the young found in nests at different seasons of the year, and with data for the number of fetuses in gravid females of unknown ages. Estimations regarding litter production and litter size differ greatly. According to various accounts (Zuschlag, '03; Lantz, '10; Miller, '11; Eaton and Stirrett, '28), wild females produce an average of from three to eight litters a year: litter size has been calculated as averaging from six to ten young (Crampe, 1884; Zuschlag, '03; Lloyd, '09; Lantz, '10; Miller, '11).

TABLE 8

Litter production and average litter size in different generations of captive gray rats

GENERATION OF BREEDING FEMALES	NUMBER OF BREEDING FEMALES	TOTAL NUMBER OF LITTERS	AVERAGE NUMBER OF LITTERS PER FEMALE	TOTAL NUMBER OF YOUNG	AVERAGE NUMBER OF YOUNG PER FEMALE	AVERAGE NUMBER OF YOUNG PER LITTER
10	54	260	4.81	1538	29.6	5.91
11	55	305	5.55	1827	33.2	5.99
12	50	312	6.24	1877	37.5	6.01
13	55	333	6.05	1906	34.7	5.72
14	56	384	6.86	2225	39.7	5.79
15	57	398	6.98	2343	41.1	5.89
16	55	492	8.95	3109	56.5	6.32
17	53	486	9.17	2986	56.3	6.14
18	58	584	10.07	3746	64.6	6.41
19	54	550	10.18	3472	64.3	6.31
20	53	437	8.25	2719	51.3	6.22
21	61	556	9.11	3329	54.5	5.98
22	58	503	8.67	2971	51.2	5.91
23	59	479	8.12	2905	49.2	6.06
24	60	555	9.25	3387	56.4	6.10
25	51	512	10.04	3232	63.3	6.31
10–25	887	7146	8.06	43572	49.1	6.10
1–25	1304	8685	6.66	53077	40.7	6.11

Females in the first nine generations of captive grays cast, on the average, 3.69 litters each, and the average litter contained 6.17 young (King and Donaldson, '29: table 7). Data for litter production and for litter size in later generations are given in table 8.

The average number of litters produced by females of the tenth generation (4.81) was greater than that of females in any preceding generation. Subsequently, litter production increased slowly until the nineteenth generation, when females cast an average of 10.18 litters (table 8). The slight decline in litter production during later generations can be attributed mainly to various changes in the location of the colony which adversely affected fertility as well as the body growth of the rats. With this rise and fall of litter production there was a corresponding change in the number of young cast, consequently average litter size in any generation did not differ materially from the mean (6.10) for the entire series (table 8). The general trend in litter production during the course of this investigation is depicted in figure 9.

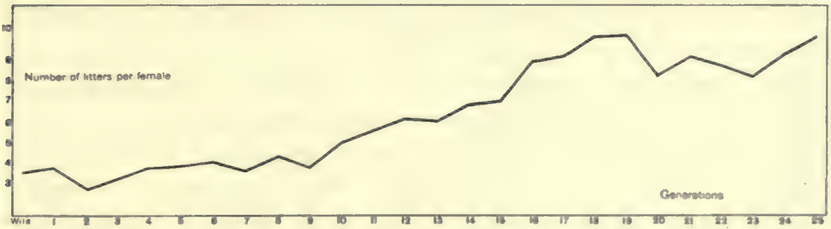

Fig. 9 Average litter production of females in different generations.

STERILITY

The infertility of wild rats brought to the colony at the beginning of this investigation and the high percentage of sterility in females of the early generations of this strain were discussed in the former report.

Later work has tended to support the hypothesis, previously advanced, that sterility in wild rats when first captured, as well as that in individuals of early generations born in captivity, was due to disturbances of the nervous system induced by fear and confinement within a limited space. The nervous tension thus produced probably influenced the activity of many organs of the body, especially those concerned with secretion, and thus indirectly affected the reproductive organs so that they were unable to function normally. As the nervous tension was lessened, after a relatively short period of captivity, the rats began to breed at a more normal rate.

During the first eight generations sterility in females decreased from 37.29 per cent to 5.88 per cent. It rose to 18.64 per cent at the ninth generation, because of the prevalence of ovarian tumors and infections of the genital tract at that time. Only five of the 161 females reared in the tenth to the twelfth generation did not breed, and in these cases sterility was caused by diseases that affected the reproductive organs. In later generations all females reared were fertile. By this time the rats had lost their fear of man and were so well adjusted to their new environment that restriction to reproduction induced by removal from their natural habitat had disappeared.

LITTER SIZE

Data for litter size in the second to the twenty-sixth generation are given in table 9. Litters of the first generation are not included in this table because of the probability that the data obtained did not cover the entire litter output of the wild females that bred while in captivity. Data for five generations are grouped together to facilitate their analysis.

The range in litter size was from one to fifteen, with the mean at six. In each of the first three groups of table 9, over half of the litters were of medium size, containing from five to seven young. The last two groups comprise a relatively smaller number of medium sized litters and more litters below or above this magnitude. This difference in the distribution of the various sized litters in the groups was due, doubtless, to the extension of the reproductive period and the increased fertility of females in the later generations (table 8).

TABLE 9

Litter size, by generation groups, in the second to the twenty-sixth generations of captive gray rats

GENERATION GROUPS	LITTER SIZE															TOTAL NUMBER OF LITTERS
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
2– 6	1	24	57	89	111	161	144	88	55	23	9	2	2			766
7–11	2	17	82	102	167	230	166	138	63	24	14	5		1	1	1012
12–16	17	71	143	241	266	370	238	193	104	62	19	4	3	1		1732
17–21	20	117	203	286	310	442	374	336	226	148	53	26	5	2	1	2549
22–26	29	114	240	299	397	463	362	276	229	116	45	27	6	2		2605
2–26	69	343	725	1017	1251	1666	1284	1031	677	373	140	64	16	6	2	8664

When the reproductive period is long, litters cast at its beginning and near its close tend to be small. Increased fertility leads not only to the production of a greater number of litters, but also, in most cases, to the casting of larger litters during the height of reproductive activity.

The summary of data in table 9 is shown by the graph in figure 10, which indicates a very symmetrical distribution of the various litter groups around the modal point.

Litter size in captive grays, as in other varieties of rats, is not affected by the season of the year in which birth occurs (King, '27). In this respect, findings for the rat accord with those for the mouse (Parkes, '26 b), the pig (Machens, '15; Carmichael and Rice, '20; Parkes, '26 a) and the dog (Dighton, '22).

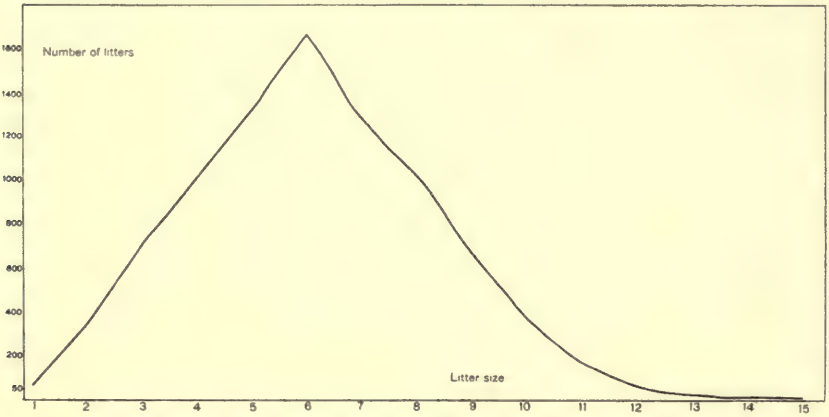

Fig. 10 Litter size in the second to the twenty-sixth generation.

Since a previous investigation has shown that the age of the mother has a pronounced effect on both litter production and litter size in rats (King, '16 a), a brief analysis of the series of data for gray rats with reference to this point is given here. Data for litters cast in the second to the twenty-sixth generation, arranged according to the age of the mothers at the time of parturition, are shown in table 10.

As indicated in table 10, comparatively few litters were cast when females were not more than 3 months of age. Although the sex organs are capable of functioning at this age, the bodies of the females are not fully grown and so less able to nourish embryos than when they are more mature. The number of litters cast increased with the age of the mothers to the period of greatest productiveness, which came when females were 7 months old, and then declined as the intervals between litters became longer. Few litters were cast after females reached the age of 20 months. Autopsies made on very old females some times disclosed embryos in the uterus that were being resorbed, probably because senility changes in the uterus so interfered with the nutrition of the young that they died at an early period of development.

TABLE 10

Litter production and litter size with their coefficients of variation in the second to the twenty-sixth generation of captive gray rats. Data arranged according to the age of the mothers at the time of parturition

MOTHERS' AGE IN MONTHS	TOTAL NUMBER OF LITTERS	AVERAGE SIZE OF LITTERS	COEFFICIENTS OF VARIATION FOR LITTER SIZE
3	238	5.42	35.0±1.08
4	437	5.98	34.4±0.78
5	518	6.29	31.9±0.67
6	566	6.33	32.5±0.65
7	620	6.37	33.5±0.64
8	608	6.55	33.2±0.64
9	608	6.38	34.0±0.66
10	596	6.40	34.6±0.67
11	559	6.06	36.6±0.74
12	533	6.14	37.9±0.78
13	535	6.37	37.6±0.77
14	493	6.00	38.8±0.83
15	512	6.10	37.5±0.79
16	468	5.93	39.6±0.87
17	419	5.98	39.9±0.86
18	419	5.72	41.6±0.97
19	306	5.29	46.6±1.26
20	130	5.20	49.2±2.05
21+	99	5.18	41.8±1.99
	8664	6.10	36.2±0.19

The average size of the litters increased until the mothers were 8 months old, when the maximum (6.55) was attained (table 10). Subsequently litter size decreased slowly, and dropped to its lowest point (5.18) at the end of the series. The rise and fall in average litter size as the age of the mother advanced is shown by the graph in figure 11, constructed from data in table 10.

A change in litter size as the age of the mother advances has been reported in other strains of rats (Crampe, 1883; Slonaker and Card, '23; King, '16 a, '24), as well as in other polytocous mammals: guinea pig (Minot, 1891; Wright, '22), rabbit (Hammond, '14), and the pig (Hammond, '14; Carmichael and Rice, '20; Keith, '30).

This series of data for gray rats, covering the litter production of a large group of females, gives 6.1 as the average for litter size. This average is the same as that found in 815 litters cast by albino females (King, '24: table 1). The norm for litter size in albinos is usually given as seven. This estimation is based, for the most part, on random samplings of litters produced in colonies where females were bred only during the most active period of reproductive life and is therefore too high, since it does not include the litters that might have been cast in the beginning and near the end of the normal reproductive period. The latter litters, as this and other investigations have shown, are usually small as compared with litters produced when females are 5 to 9 months old.

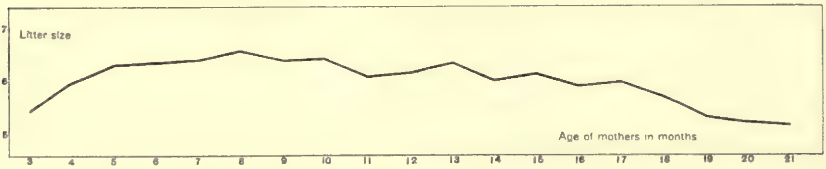

Fig. 11 Age of the mothers and litter size in the young.

Variation in litter size was high regardless of the age of the mothers, as is indicated by series of coefficients of variation given in table 10. Variation changed considerably, however, as the age of the mothers advanced. It was slightly below the mean in litters cast when females were very young, and significantly lower when females were at the height of reproductive activity at 5 to 9 months of age, deviations being more than three times their probable errors. When fertility began to decline, variation in litter size increased gradually, reaching its highest point in litters produced near the end of reproductive life. These changes in the variation of litter size as the age of the mothers advanced are very similar to those reported by Little ('33) in a strain of inbred mice.

The age of the female, seemingly, is a factor that profoundly influences her entire reproductive life. It determines to a great extent not only the beginning and the end of her sexual activity, but also produces cyclic changes in litter production, in litter size, and in the variation of litter size. It may prove, also, to have an effect on the functioning of the germ cells, as Little ('33) has suggested is probable.

THE SEX RATIO

Little is known regarding the sex ratio in gray rats living in their natural habitat. The proportion of the sexes found in large numbers of trapped adults gives no information of value on the sex ratio in the newborn, since mortality during early postnatal life may have taken a heavier toll of one sex than of the other.

Two small series of data have been recorded that give the sex proportions in the young of wild females brought into captivity: Miller ('11) found a sex ratio of 82.1 males to 100 females in fifty-one offspring of a caged wild female; the sex ratio in 139 young obtained at the beginning of this investigation from matings of wild rats was 98.6 males to 100 females. This evidence, meager though it is, indicates that a sex ratio below equality may be normal for wild rats. Since these animals are polygamous, a preponderance of females among them would not be detrimental to the survival of the race.

Sex ratios for individuals in the first ten generations of captive grays were given in the former report on this strain, and discussed with reference to various factors that might have influenced them. Data for sex distribution and for sex ratios in rats of later generations are given in table 11.

The sex ratios in table 11 are discordant, and do not show any definite trend as the generations advanced. In many cases a high ratio in one generation is followed by a relatively low ratio in the succeeding generation, and there are no significant differences between ratios for successive generations nor between any one ratio and that for the series as a whole. The ratio for individuals in the eleventh to the twenty-sixth generations is but slightly higher than that for the first ten generations, and for the combined series is below equality, being 97.3 males to 100 females.

TABLE 11

Sex distribution and sex ratios in the eleventh to the twenty-sixth generation of captive gray rats

GENERATION	TOTAL NUMBER OF INDIVIDUALS	MALES	FEMALES	NUMBER OF MALES TO 100 FEMALES
11	1538	752	786	95.7±3.27
12	1827	946	881	107.4±3.39
13	1877	953	924	103.2±3.21
14	1906	907	999	90.7±2.81
15	2225	1128	1097	102.8±2.94
16	2343	1171	1172	99.9±2.78
17	3109	1561	1548	100.8±2.44
18	2986	1458	1528	95.4±2.36
19	3746	1823	1923	94.3±2.08
20	3472	1716	1756	97.7±2.24
21	2719	1311	1408	93.1±2.42
22	3329	1659	1670	99.3±2.32
23	2971	1495	1476	101.3±2.51
24	2905	1412	1493	94.6±2.37
25	3387	1634	1753	94.5±2.19
26	3232	1572	1660	94.7±2.25
11–26	43572	21498	22074	97.4±0.63
1–10	9505	4680	4825	96.9±1.34
1–26	53077	26178	26899	97.3±0.57

Figure 12 shows graphically the sex ratios for the first twenty-six generations of captive grays.

The lowest point in the graph of figure 12 is at the second generation, where the sex ratio falls to 81.9 males to 100 females. Thereafter the graph tends to rise, reaching its highest point (107 males to 100 females) at the twelfth generation, then declining gradually and ending in a nearly straight line which is below the level of the mean. A male excess among individuals is indicated at only eight of the twenty-six points in this graph, and there are no changes in it, except possibly the drop near its beginning, indicating that captivity per se affected the ratios in any way.

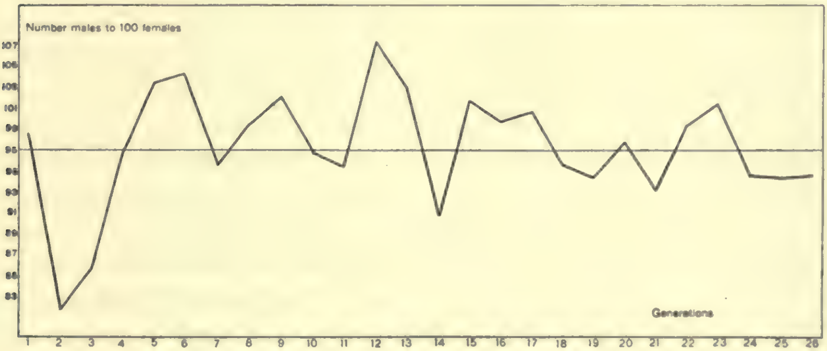

Fig. 12 Sex ratios in different generations.

Data for a series of stock albino rats, comprising the litter output of a group of individuals reared under the same conditions of environment and of nutrition as the early generations of captive grays, give a mean sex ratio of 105.2 ± 2.00 (King, '24). This ratio is significantly higher than that found in gray rats, the difference being 7.9 ± 2.08. The disparity in the sex ratios of these two strains must be due either to errors in recording the data or to differences inherent in the strains, since they cannot be ascribed to unlike conditions of life.

Depletion of litters through destruction of stillborn young by adults in the cage is the most common source of error in litter records for rats. Such errors cannot be avoided, since parturition often occurs at night and some hours may elapse before the young are examined, but they have relatively little effect on a large series of litter data, since the stillborn form but a small percentage of the young cast, as a rule. In 968 litters of gray rats obtained at birth and known to be complete, the stillborn comprised but 1.2 per cent of the 6295 individuals (King, '35). This finding accords well with that of 1.3 per cent stillbirths in 31,670 albino rats (King, '21). Since only 0.05 per cent stillbirths were recorded through the first twenty-six generations of gray rats, it is possible many stillborn young were devoured by adults in the cage before the litters were examined. In a former paper (King, '21) it was estimated that the normal percentage of stillbirths in any strain of rats reared under favorable conditions of environment and nutrition is probably not greater than 2 per cent. If, therefore, the number of young in the final summary of table 11 is increased to include 796 (1.5 per cent) stillborn young that, conceivably, might have been omitted from the records, with the sexes proportioned to give approximately the ratio among the 268 stillborn young recorded for the strain (111.8 males to 100 females), the data so adjusted would raise the final sex ratio in table 11 from 97.3 to about 97.5 males to 100 females. Obviously the low sex ratio found in gray rats cannot be ascribed to the omission of stillborn young from the records, unless the number of such individuals greatly exceeded 2 per cent of the total and the sex ratio among them was unusually high. There are no valid grounds for either of these assumptions.

In an investigation of the factors controlling fertility in the rabbit, Hammond ('14) found that the number of atrophic fetuses in females of various domesticated breeds greatly exceeded that found in gravid wild females. He suggested that possibly one of the effects of domestication on this animal has been to increase the number of ova shed at each period, and at the same time to reduce the proportion of those which develop. In the gray rat, captivity over a considerable period of time has greatly increased fertility, but has not changed average litter size (table 8). If the number of ova shed at each period has been increased by domestication, then fetal atrophy has increased also, or average litter size would not remain constant. It is known, from the investigations of Huber ('15) that many rat fetuses die soon after implantation. Such fetuses, as well as those that die at later stages of gestation, are absorbed in situ and not aborted as in higher mammals, therefore the proportion of the sexes among them cannot be determined.

Recent work in genetics has thrown much light on the cause of fetal mortality, by showing that germ cells frequently contain lethal or semi-lethal genes that either kill the embryos carrying them, or so reduce their vitality that they rarely survive. Such deleterious genes have been reported in mice (Little, '19; de Aberle, '27; Hagedoorn and Hagedoorn, '28; Chesley, '35; Kamenoff, '35) and in the rabbit (Hammond, '33). An assumption that germ cells of gray rats contain genes that tend to kill or greatly reduce the vitality of embryos, particularly males, would offer a plausible explanation for the low sex ratio among the newborn.

Since the sex ratio in gray rats is significantly lower than that in albinos, it may be of interest to compare the sex ratios in white races of man with those for colored races, chiefly of negro descent, when these races live side by side under the same topographical and climatic conditions, as shown in table 12. This tables is based on one given by Parkes ('26), augmented by the inclusion of stillbirths in some entries. The probable errors of the sex ratios are given when the data seem to be sufficiently accurate to warrant their calculation. To this table has been appended the sex ratio for captive gray rats (table 11) and that for the series of albino rats maintained under the same environmental and nutritive conditions (King, '24: table 1).

In all groups cited in table 12 the sex ratios for black races are lower than those for white races. When judged by their probable errors, differences between corresponding ratios are significant for the data from Heape ('09) and from Little ('20), but not for data given by Nichols ('07). Jastrzebski's ('19) data, given in round numbers, cannot be considered as reliable as those from other sources. In these groups, differences between the ratios are probably not important, except in the data from the U.S.A. Parkes ('26) states that the lower sex ratios in black races seem to be a general phenomenon that probably has some real basis. He considers it due to greater prenatal mortality in the blacks, among whom abortions and stillbirths are greater than in white races. The sex ratio in man, as in other mammals, seems to be one of the characteristics of the race that depends upon a number of factors, some of which are genetic, others physiological or environmental. It is not improbable that the genetic constitution of a race may prove to be one of the most important of the various factors that affect the vitality of fetal young and so largely determine the sex ratio among the newborn.

TABLE 12

Sex ratios in white and in colored races of man

AUTHORITY	LOCALITY	WHITE RACES		COLORED RACES	
		Number of individuals	Number of males to 100 females	Number of individuals	Number of males to 100 females
Heape, '09	Cuba	70684	108.4±0.39	21028	101.1±0.67
Little, '20	New York	1834	118.3±1.71	1418	96.1±1.76
Nichols, '07	District Columbia	71024	107.3±0.54	56034	105.8±0.60
Jastrzebski, '19	Cape Colony	100000	105.4	100000	102.6
	U.S.A.	700000	105.7	12000	100.0
	New York	700000	104.5	10000	101.6
	New Orleans	12000	102.0	4000	98.2
	District Columbia	20000	105.0	9000	100.0

Sex ratios in albino and in gray rats

		ALBINO RATS		GRAY RATS	
King, H. D.	Wistar Inst. colony	4992	105.2±2.00	53077	97.3±0.57

The hypothesis that litter size affects the sex ratio in polytocous mammals is one of long standing, and various series of data have been recorded both for and against it. An arrangement of data for gray rats to indicate the relation between litter size and the sex ratio is shown in table 13.

Litters containing more than twelve young are included in table 13 merely to complete the records. They are too few to be of value statistically, and the ratios are not in accord with those for other litter groups.

The great majority of litters in this series contained from four to eight young, and the sex ratios for these groups vary little from each other or from the ratio for the series as a whole. In litters of one and in litters containing eleven or twelve young the sex ratios are considerably lower than those for the other litter groups, but the differences are not important statistically. Data in table 13 do not indicate any definite relation between litter size and the sex ratio in gray rats, and so are in agreement with the findings for many other mammals: albino rat (King and Stotsenburg, '15; mouse (Parkes, '26 b); deer mouse (Sumner, McDaniel and Huestis, '22); guinea pig (Ibsen, '22; Schott and Lambert, '30; Haines, '31) and the pig (Parker and Bullard, '13; Machens, '15; Parkes, '23).

TABLE 13

Litter size and the sex ratio in the second to the twenty-sixth generation of captive gray rats

LITTER SIZE	NUMBER OF LITTERS	NUMBER OF INDIVIDUALS	MALES	FEMALES	NUMBER OF MALES TO 100 FEMALES
1	69	69	33	36	91.7±14.94
2	343	686	340	346	98.3± 5.06
3	725	2175	1061	1114	95.2± 2.75
4	1017	4068	2027	2041	99.3± 2.09
5	1251	6255	3048	3207	95.0± 1.62
6	1666	9996	4989	5007	99.6± 1.34
7	1284	8988	4437	4551	97.5± 1.38
8	1031	8248	4089	4159	98.3± 1.46
9	677	6093	2974	3119	95.4± 1.65
10	373	3730	1844	1886	97.8± 2.16
11	140	1540	739	801	92.3± 3.17
12	64	768	362	406	89.2± 4.34
13	16	208	112	96	116.7±10.95
14	6	84	42	42	100.0±14.73
15	2	30	12	18	66.6±16.74
1–15	8664	52938	26109	26829	97.3± 0.57

It has been shown that in each of four different strains of rats the sex ratio changed in a similar way as the litter series advanced (King, '24: table 8). This finding seems to indicate that the age of the mother has some influence on the sex ratio in her newborn young. As a further test of this assumption, litter data for gray rats were arranged according to the age of the mothers at the time of parturition, and the sex ratios calculated. The series of ratios thus obtained is given in table 14.

TABLE 14

Sex distribution and sex ratios in the second to the twenty-sixth generation of captive gray rats. Data arranged according to the age of the mothers at the time of parturition

MOTHER'S AGE IN MONTHS	TOTAL NUMBER OF INDIVIDUALS	MALES	FEMALES	NUMBER OF MALES TO 100 FEMALES
3	1291	661	630	104.9±3.94
4	2613	1322	1291	102.4±2.70
5	3262	1633	1629	100.2±2.37
6	3582	1758	1824	96.4±2.17
7	3955	1965	1990	98.7±2.12
8	3984	1977	2007	98.5±2.10
9	3881	1923	1958	98.2±2.11
10	3815	1885	1930	97.7±2.13
11	3389	1716	1673	102.6±2.37
12	3277	1647	1630	101.0±2.38
13	3309	1641	1668	98.4±2.25
14	2960	1407	1553	96.6±2.26
15	3126	1542	1584	97.4±2.34
16	2777	1331	1446	92.1±2.36
17	2510	1226	1284	95.5±2.57
18	2397	1169	1228	95.1±2.62
19	1620	751	869	86.4±2.90
20	677	314	363	86.5±4.49
21+	513	241	272	88.6±5.28
	52938	26109	26829	97.3±0.57

Males outnumbered females in litters cast when mothers were from 3 to 5 months of age, and also in litters born when the mothers were 11 and 12 months old. At all other age periods of the mothers litters contained an excess of females, this excess being most marked in offspring produced near the close of reproductive life (table 14). The change in the sex ratio as the age of the mother advanced is shown by the graph in figure 13, which was constructed from data in table 14.

Beginning relatively high, the graph in figure 13 falls gradually for a time, rises again at the middle of its course, and then declines until its end. This cyclic change in the sex ratio with the advancing age of the mothers is very similar to that found in the four strains of rats, mentioned above, where data were arranged by parity. The accord in these various series of ratios can hardly be a matter of chance, although in none of them are differences between the ratios in various groups important when judged solely by their probable errors.

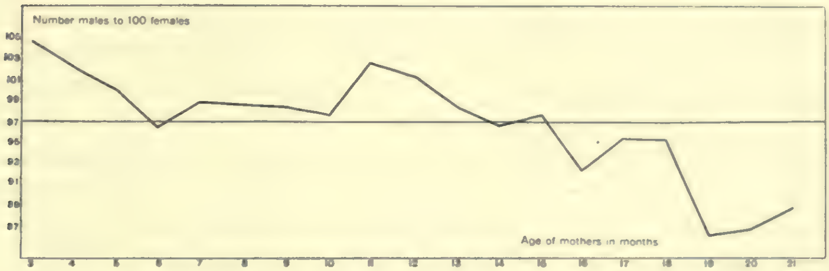

Fig. 13 Age of the mothers and the sex ratio in the young.

Few of the studies on lower mammals in which data have been analyzed with reference to the relation between the age of the mothers and the sex ratios in the young have given consistent results, since the data were obtained, for the most part, by the method of 'random sampling,' and therefore do not cover the complete breeding records for a given group of females. Investigations on the guinea pig, made by Ibsen ('22), showed a difference of 6.06 times the probable error between the sex ratio in young from mothers 8 months old and that in offspring of females 15 months of age. In later data obtained from this animal, Ibsen and Burhoe ('28) found no relation between the age of the mother and the sex ratio in the young, "thus furnishing proof that results biometrically significant do not always receive biological verification." The more extensive series of data for the guinea pig, given by Kröning ('34), shows that the sex ratio tends to decrease as the age of the mother advances. This investigator explains his findings in accordance with the old Hofacker-Sadler hypothesis that the sex ratio in the young is influenced by the relative age of the parents.

In the large and carefully compiled series of data for Flemish and for Swedish breeds of cattle, summarized by Johansson ('32: table 6), the general trend of the sex ratio in each series is cyclic, and much like that in table 14, except that the ratios are relatively low in the early born young. In Johansson's series, as in these for gray rats, differences between ratios are not important statistically, therefore the findings can be considered merely as suggestive.

Literature contains numerous references to investigations on the sex ratio in various races of man, based chiefly on data from governmental registrations of vital statistics and on geneological or hospital records. In many of these studies the results accord in showing that the sex ratio is very high for first births and then tends to fall as the age of the mother advances (Düsing, 1884; Rosenfeld, '00; Newcomb, '04; Punnett, '04; Lewis and Lewis, '06; Siegel, '17; Parkes, '24, etc.). The usual explanation given for this change in the sex ratio is that there is an increase in the prenatal mortality of males as the mothers grow older, but why this increased mortality occurs is not known. Age changes in body metabolism, in the structure of the uterus or in hormone secretions affecting reproductive processes probably affect the vitality of fetal young, and may tend to eliminate more males than females. However, until more light has been shed on the effect of such factors, it will be useless to speculate as to the cause for the change in the sex ratio of the young as the age of the mother advances.

MORTALITY

No attempts were made to determine the potential duration of life in gray rats, since it seemed more important to ascertain the condition of various body organs before senility had altered them.

In all generations, the study of life processes was terminated when rats reached the age of 20 months, and a stated number of individuals given to Doctor Donaldson for a determination of organ weights. Exceptions were made in the case of females that were unusually vigorous and had cast litters when they were over 19 months of age. Such females were housed with young males, and not killed until their reproductive activity had ended in order that the series of litter data might be complete.

Mortality at birth was very low in all generations, and only 268 stillbirths were recorded among the 53,077 young born in the first twenty-six generations. Mortality among the young during the suckling period decreased considerably after the tenth generation. By this time females were so well adjusted to conditions of captivity that they rarely destroyed their offspring returned to the nest after they had been removed for examination, and nests were less frequently disturbed by other inmates of the cage. Offspring were destroyed or neglected only when the mother was in poor physical condition, or when one or more of her nipples had been injured by the young when suckling.

Table 15 gives mortality data for the eleventh to the twenty-fifth generation, with a summary of the records for the entire series grouped to indicate the general trend in mortality rate as the generations advanced.

In later generations the mortality rate in both sexes was low during the first year of life, the relatively high percentage (11.9) in the twenty-third generation being due to the accidental killing of four young females (table 15). Mortality increased greatly after the rats were a year old, and only 79.9 per cent of males and 76.6 per cent of females lived to the age of 20 months.

TABLE 15

Mortality in various generations of captive gray rats

GENERATIONS	MALES					FEMALES				
	Number of individuals	Number living at 12 months	Number living at 20 months	Per cent mortality at 12 months	Per cent mortality at 20 months	Number of individuals	Number living at 12 months	Number living at 20 months	Per cent mortality at 12 months	Per cent mortality at 20 months
11	54	52	42	3.7	22.2	57	56	45	1.8	21.1
12	52	49	37	5.8	28.8	52	50	39	3.8	25.0
13	55	52	45	5.5	18.2	56	53	39	5.3	30.4
14	55	52	43	5.5	21.8	56	55	41	1.8	26.8
15	53	48	42	9.4	20.8	57	55	39	3.5	31.6
16	61	59	50	3.3	18.0	55	55	44	0.0	20.0
17	55	50	44	9.1	20.0	55	52	42	5.5	23.6
18	57	52	43	8.8	24.6	58	58	49	0.0	15.9
19	54	53	48	1.9	11.1	54	54	41	0.0	24.1
20	56	55	46	1.8	18.2	53	51	39	3.7	26.4
21	54	51	42	5.6	22.2	61	59	47	3.3	22.9
22	57	57	47	0.0	17.5	58	56	46	3.4	20.7
23	60	58	49	3.3	18.3	59	52	41	11.9	30.5
24	59	56	44	5.1	25.4	60	60	50	0.0	16.6
25	50	50	43	0.0	14.0	51	50	43	1.9	15.7
1–10	521	502	321	3.6	38.4	542	521	339	3.9	37.4
11–15	269	253	209	5.5	22.3	278	269	203	3.3	26.9
16–20	283	269	231	4.9	18.4	275	270	215	1.8	21.8
21–25	280	272	225	2.8	19.7	289	277	227	4.2	21.5
1–25	1353	1296	986	4.2	27.1	1384	1337	984	3.4	28.8

The summary of data in table 15 shows no general trend in the mortality rate at 12 months in either sex. In males, the lowest rate (2.8 per cent) comes for individuals in the last group, while in females the rate for this group is high (4.2 per cent) only because of accidental deaths. In both sexes, however, the mortality at 20 months tended to decrease as the generations advanced. In males of the last group, mortality was 18.7 per cent below that in the first group; in females it was 15.9 per cent less. Conditions of life in captivity thus tended to prolong the average life span of the individuals, possibly because they received more adequate nutrition and were protected from various diseases prevalent among wild rats living in their natural habitat.

The main causes of death among older individuals were the lung infection, commonly called 'pneumonia,' and tumors of various kinds. Pneumonia rarely attacks rats until they are a year old, and males seem more susceptible to it than females. Autopsies made on rats 20 months old have shown very few individuals that were entirely free of this disease. Tumors occur mainly in females, and are usually found in the ovaries or mammary glands. The latter growths, when small, can be removed easily, and rarely return. Cancer has appeared but rarely in this strain, as it has been found only in one male and in three females. Gray rats are very resistant, apparently, to the middle-ear infection commonly found in other strains of rats. Only eight of 2737 individuals reared for study developed this disease, and in two of these cases it could be attributed to the fact that gray females were serving as 'foster mothers' to young from an albino strain in which many individuals were affected.

BEHAVIOR

After 14 years of life in captivity the behavior of gray rats had changed so greatly that many of the obnoxious traits exhibited by the early descendants of feral animals had disappeared. These changes in behavior occurred so slowly, however, that there was no noticeable difference in the conduct of individuals in any two succeeding generations, although a comparison of the behavior of rats in early and in late generations indicates clearly the striking modifications that occurred.

A high nervous tension and extreme fear of man was shown by all rats in early generations. They ran wildly about the cage even at the approach of colony workers to whom they were accustomed, and constantly gnawed the wire netting and other parts of the cage in their efforts to escape from confinement. When the cage door was opened the rats often jumped directly at the face of the person who thus seemed to offer them a way to freedom. An escaped rat, when captured, showed marked evidence of fear, trembling and clicking its teeth, and sometimes on being returned to the cage lay inert for a few moments and then died. At this time considerable difficulty was experienced in rearing the young. If a nest was disturbed at or soon after the birth of a litter, the mother usually destroyed her offspring. If the members of a litter were removed from the nest, even when they were several days old, only the exceptional females would care for them on their return. Many litters, therefore, had to be reared by foster mothers from other strains.

After the rats had become adjusted to new conditions of life, their fear of man and nervous tension decreased greatly. A rat that escaped from the cage displayed little resistance on being captured, and its behavior was normal when it rejoined the family group. As a rule, rats remained quiet when the cage door was opened, even when they were being inspected by strangers. Many of them came to the front of the cage at the approach of the feeding truck, and would take food offered through the wire netting of the door. Females no longer resented inspection of their offspring, and took excellent care of them. If newborn young were removed from the nest for examination, they would be cared for on their return. Many females would rear litters from other strains if they were barred from the nest until the young had acquired the nest odor. However, alien young were always killed if the female had access to them as soon as they had replaced her own offspring.

Two of the outstanding traits exhibited by individuals in early generations still persisted at the twenty-fifth generation. Adults continued to show pronounced antipathy to individuals from other litters placed in their cage, and promptly attacked and usually killed them unless special precautions were taken, as described in the previous report. Even these devices were not always effective. This treatment of strangers seems to indicate a retention of the primitive instinct to protect the nest from all entrants not members of the family group. The 'killer' instinct, discussed in a previous section, has been shown by gray rats of all generations, especially by large males. This trait is doubtless of advantage to the species, since the elimination of smaller and weaker individuals insures that the largest and most vigorous animals will be the progenitors of the succeeding generation. In late generations it was no longer necessary, though often expedient, to stupefy rats with ether when they were removed from the cage for weighing, as they could be picked up by the tail with long forceps but not with bare hands.

As this investigation was designed to study the effects of captivity on gray rats, no attempts were made to tame any of the rats used in this work so that they could be handled as are the rats of various strains maintained for general laboratory purposes. While captivity over many years had accustomed these rats to receiving their food from man and to his presence, their innate fear of him did not decrease to the point where they would willingly submit to being held by bare hands. Gray rats can be tamed more easily, perhaps, than any other feral animals, if one has the required patience and understanding of their temperament. Two young rats from the third generation were taken to another colony by Miss Ruth Meeser, of The Wistar Institute, and rendered so tame that they showed no vicious traits when adult, although they were always nervous in the presence of strangers and could be handled only by Miss Meeser. More recently, a number of young gray rats were given to Miss Meeser for taming, and she succeeded in making them quite as gentle as are stock albinos. These tamed rats were then used in experiments requiring daily injections of solutions through the abdominal wall. They submitted to these injections as readily as do albinos, even though they were held by bare hands. Gray rats, therefore, can now be used for all forms of experimental work. Large, vigorous, and seemingly little susceptible to certain diseases prevalent in other strains of rats, they should be valuable for laboratory work in which it seems desirable to use individuals from a pure strain of known ancestry.

MUTATIONS

Several mutations affecting the color or the structure of the hair appeared in captive gray rats during the period covered by this report. As only a brief report of these mutations has been published (King, '32), a more detailed account is given here, including genetic studies made to determine the mode of inheritance of certain types.

One of the six wild gray females (2) used as foundation stock for the colony had a small spot of white hair on the ventral surface of the body between the forelimbs, similar in size and position to the spot shown in figure 14. This female was mated with a wild male (2), presumably a brother since the two rats were trapped at the same time and appeared to be the same age. From the matings of this pair of rats twenty-nine young were obtained, of which seventeen had a patch of white hair on the ventral surface varying in size from a mere dot to a spot no larger than that in figure 14. Experiments were then begun to determine whether the amount of white in coat could be increased by selective breeding. For two generations rats having white spots were inbred, brother and sister. Subsequent matings were made between individuals with the greatest amount of white in their coats, regardless of their relationship.

During early generations there was but little increase in the size of the white area, but in the sixth generation individuals appeared with irregularly shaped patches of white covering the space between the forelimbs (fig. 15). Later the white was extended, and in some cases a second white spot appeared (fig. 16). Matings of these rats produced some offspring with a long streak of white in the midventral region of the body (fig. 17). In the fifteenth generation a litter was obtained in which three of the individuals, one male and two females, were typical 'Irish' rats in that the four feet, the tip of the tail, and the ventral surface were covered with white hair (fig. 18). Presumably at this point the self factor (H) changed to its allelemorph (h^1), a reverse change to that found in experiments made by Castle and Phillips ('14) with hooded rats where the hooded factor (h) changed to h^1. When 'Irish' rats were inbred they produced some offspring like themselves and others in which the white area was extended up the sides of the body (fig. 19). Descendants of the latter rats had coat patterns showing but slight variations from that in figure 20. Gray hooded rats were kept in the colony for some 3 years, but no further attempts were made to increase the amount of white in the coat through selective breeding. Matings of these rats with black hooded rats from a strain that had bred true to type for many years produced only gray hooded young, indicating that the hooded pattern in the two strains was due to the same gene mutation.

Some years ago Castle and Phillips ('14) carried out an extensive series of experiments in order to study the effects of selection on the coat pattern of black hooded (piebald) rats. These experiments, which were continued through twenty generations, were divided into two series; in one series selection was made in a plus direction, and in the other series in a minus direction. At the end of the experiments individuals in the plus series were black except for a small area of white on the ventral surface, similar in its position to the spot shown in figure 14. In individuals of the minus series black was restricted to the head region. Castle's ('19) final conclusions regarding the results of this work were that alterations in the coat pattern were not due to changes in the gene for the hooded pattern, but to residual heredity. Selection had utilized the minor genetic changes that are occurring continually to "move the racial mode and mean either in a plus or in a minus direction without encountering impassible limits short of an all white or an all black condition" (Castle, '31).

In light of Castle's work, it seems probable that a hooded mutation occurred at some period in the ancestry of the wild rats from which gray hooded rats were derived by selective breeding. Evidently breeding under natural conditions, and the action of plus modifiers, had kept recessive the hooded pattern in the wild stock, but not effaced the gene for spotting which manifested its presence only in the coat of the female, as the male with which this female was mated had no white in his hair. By selective breeding through a number of generations plus modifiers were gradually eliminated, or rendered inactive, and the white area increased until the typical hooded pattern was restored.

Aside from the hood strain, developed among the descendants of one pair of wild rats, captive grays bred true to type, as far as known, for a period of 7 years, during which time over 10,000 young were born and many hundreds of them reared to an age when coat characteristics were well defined.

In the eleventh generation one of four females, mated to a brother, cast a total of forty-five young of which eleven died at or a few days after birth so their coat color could not be determined. The remaining thirty-four individuals comprised twenty-four normal grays and ten mutant blacks. The first mutant, a male, appeared in a litter of four, born when the mother was 15 months old. Although sisters of the female that cast black young were mated to the same sire, no mutants appeared among their progeny, nor has this mutation appeared a second time in the strain. These mutants were a very intense black on the dorsal side of the body, and a dark slate color on the ventral side. There was no change in their color for a period of about 4 years. Then individuals appeared in which white hairs were scattered through the coat and among the vibrissae. These white hairs were especially numerous on the sides of the body, and in some cases were found in groups of three to six. Possibly a 'silver' mutation occurred in these rats, similar to that found in the mouse (Dunn and Thigpen, '30), but no genetic tests of this assumption were made. Later the hair in some individuals had a distinctly brownish tinge, but inbreeding through several generations did not change the coat color to that of the non-agouti brown or chocolate rat.

Routine examination of newborn litters of the thirteenth generation disclosed three individuals in which the eye color seemed somewhat lighter than that normal for gray rats. Rearing these rats, which belonged in a litter cast when the mother was 16 months old, revealed a second mutation in the strain, ruby-eyed dilute. Two more of these mutants appeared in a later litter from the same parents, making a total of five mutants in thirty-four young. Normal young from these litters were reared and used for breeding. As expected, a number of ruby-eyed dilutes appeared among their descendants in later generations. Matings of these mutants with ruby-eyed descendants of the first rats of this type, which were discovered by Whiting (Whiting and King, '18), gave only ruby-eyed dilute young. These two mutations from unrelated gray stocks were due, therefore, to the same recessive gene which dilutes pigmentation in the eyes as well as in the coat.

A third mutation, albinism, was discovered in two rats of the fourteenth generation through the color of the eyes at birth. These mutants were members of the fifth litter cast when the mother was 14 months old. There were no other mutants among her forty-five offspring. Sisters of this female mated to other males produced only gray young, but albinos were found among their descendants during several succeeding generations.

The next mutation found, curly (Cu), was a type not previously recorded in rats, although subsequently two mutations, phenotypically similar but genetically different, were discovered; kinky (k) by Feldman ('35), and curly$_2$ (Cu$_2$) by Gregory and Blunn ('36). Curly is a dominant mutation that affects hair structure, not its color. It eliminates or greatly

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reduces the size of the guard hairs with the exception of a few around the head, and causes a bend or twist in all hairs of the body including the vibrissae. Because of the modification of the vibrissae, this mutation can be detected in very young rats. The characteristic curl of the hair becomes very pronounced when the rats are 2 weeks old (fig. 21), and the vibrissae are then spiral or bent inward and hooked at the ends (fig. 22). When the rats are about 25 days old the curl begins to disappear and soon the coat looks much like that in normal rats, although it has a soft downy appearance because of the absence of guard hairs (fig. 23). This change in the coat is due probably, as Feldman ('35) has suggested, to the fact that the vigorous pelages of young adults are able to overcome in a large measure the destructive effects of the gene.

The curl reappears in the hair of the mid-dorsal surface when the mutants are about 7 months old (fig. 24), and in the course of 2 or 3 months has extended over the entire coat. This mutation shows its most pronounced effects in old rats where the entire dorsal surface is covered with very curly hair (fig. 25). On the ventral the longer hairs tend to break off or to disappear in various places, thus showing patches of skin between ridges of curly hair (fig. 26).

A histological examination of sections of the skin of curly mutants of various ages disclosed no apparent abnormality in the hair follicles. The wavy appearance of the coat seems to be due to the fact that at intervals along the shaft the cortical layer of the hair becomes very thin, and a bend or a twist occurs at these points.

This mutation was first discovered in a male of the seventeenth generation, born when the mother was 6 months old. Early changes in the pelage had not been noted, but the unusual appearance of the coat when the curl had returned after the 'latent' period aroused suspicion that a new mutant type had appeared. Fortunately, this male had sired a litter which had been saved for study. The four females in this litter had normal coats; the two males were curly. Nine litters were obtained from the matings of these curly males with five normal gray females, two of which were their sisters. These litters contained sixty-two young of which eight were stillborn. Of the fifty-four living young, twenty-five were curly and twenty-nine were normal. The proportion of normal and mutant young was thus near the 1 to 1 ratio to be expected when one parent is a heterozygous dominant. Normal rats from these litters, when inbred, produced only normal young. Breeding the curly rats inter se gave eighty-nine litters with a total of 544 young of which twenty-eight were stillborn. As many of the young died shortly after birth, coat characteristics could be determined for only 266 individuals, of which 181 were curly and 85 normal. Among the curly rats there were 82 males and 99 females, so the mutation is autosomal and not sex linked. The number of curly rats in these litters was below the number (199) to be expected, but doubtless there was an excess of curly rats among the individuals that died young, since these mutants showed the same lack of vitality and vigor that has been found in other mammals in which morphological variations have appeared.

From the breeding tests described above it is evident that curly is a mendelian dominant differing from smooth coat by a single gene. Rats heterozygous for curly show the mutant characteristics in a somewhat less degree than do homozygotes. In them the period when the coat is barely distinguishable from that in normal grays is longer, and in older animals the wave in the hair is less pronounced than it is in homozygotes of like age.

A strain of curly mutants was developed for study and for experimental use. In the early generations curly rats were much inferior to normal grays in fertility and in vigor, and mortality among the young was excessive. After sufficient mutants were available to make possible a rigid selection of breeding stock there was a marked increase in fertility, mortality among the young decreased, and adult individuals compared favorably with normal grays in size and vigor.

Structural modifications that produce curly or wavy hair occur in many mammals, including man. When the hair becomes very curly or wooly, the gene responsible has been found to be a dominant, as is the case in various ulotrichous races of man, in European races of white stock (Mohr, '32; Schokking, '34), in karakul sheep (Macalik, '32; Tänzer, '32), in swine (Rhoad, '34), in caracul mice (Carnochan, '37; Dunn, '37), as well as in curly and curly$_2$ rats (King, '32; Gregory and Blunn, '36). On the other hand, if the wave in the hair is slight or tends to disappear with advancing age, the mutation, seemingly, is always a recessive, as in the rex rabbit (Castle, '29), kinky rats (Feldman, '35), and wavy mice (Crew, '33; Keeler, '35).

After the appearance of the curly mutation it was decided that an accumulation of mutant genes in the stock was undesirable, since such genes might possibly affect growth or other life processes in individuals carrying them. Therefore, from the eighteenth generation, all litters reared were offspring of parents that, according to the breeding records, did not carry any of the mutant genes known to be present in the strain. To facilitate the elimination of such genes, individuals in all litters reared in the twenty-first to the twenty-fifth generations were inbred brother and sister.

No new mutations appeared in the strain until the twenty-second generation, when several rats, offspring of brother and sister matings, were found to have more brown pigment in their coats than is present in typical gray rats. Inbreeding these rats gave young of which approximately one-fourth were brown agouti, or cinnamon. This mutation had not been reported previously in rats, although it was known in other rodents (Castle, '31). Breeding tests showed that cinnamon is a simple mendelian recessive, in which brown pigment replaces black throughout the coat (King, '32). Crossing cinnamon rats (AbCH) with pure blacks (aBCH) gave only normal gray young. Inbreeding the F$_1$'s from this cross gave non-agouti brown or chocolate rats (abCH).

Captive grays have bred true to type since the appearance of the cinnamon mutants. However, two other variations from the normal type have been found in mutant strains, aside from the possible 'silver' mutation in black rats. The waltzing character (w), long known in mice (Yerkes, '07) and reported in other species of rats by Bonhote ('12) and by Hagedoorn and Hagedoorn ('22), appeared in the fourth generation of mutant albinos (King, '36). Another new mutation, which has been designated 'stub' (st), was found in the eighth generation of cinnamon rats. Stub is a simple mendelian recessive that has a very deleterious effect when in a homozygous condition. It reduces the number of tail vertebrae, frequently produces malformations in the posterior region of the body, markedly affects the viability of the young and greatly retards body growth in individuals that survive. A full account of this mutation will be published elsewhere.

There is little in the breeding history of gray rats to support an assumption that genes for these various mutations were present in the foundation stock and remained latent until chance matings brought them to light. The hooded gene, as shown above, was carried by one pair of wild rats (female 2: male 2), so this mutation requires no further comment. All other feral rats that bred in captivity produced only normal gray young, as far as known. The F_1 generation comprised twenty-one litters containing 139 young, of which 106 were raised to maturity. These litters, as well as those born in later generations, were carefully examined at or soon after birth, in order to detect any structural anomalies or any variations in coat color that might be disclosed through changes in eye pigmentation, such as albinism or ruby-eyed dilute. Since black rats cannot be distinguished from grays until the pelage develops, this mutation might have escaped detection in early generations.

Although most of the offspring of wild rats were reared by albino foster mothers, all of them were as savage and as difficult to care for as were their parents. Tests made indicated that individuals that had been reared apart would not always live together amicably when adult. Therefore, to avoid the loss of valuable animals, it was deemed advisable to keep members of the same litter together, whenever it was possible to do so. All F_1 individuals were inbred, brother and sister, with the exceptions noted below. Aside from the rats carrying the hooded gene, no mutants were found among the 857 individuals comprising the F_2 generation. Any simple recessive color genes present in the foundation stock would have manifested their presence in the second generation, unless they were carried by female 1 and her mate, whose offspring could not be inbred.

It may be of interest to record some data regarding the first pair of wild rats, since their descendants have been dominant in the strain from early generations. Female 1 was brought to the laboratory in February, 1919, having been trapped in an abandoned stable in the outskirts of Philadelphia. She was approximately 6 months of age when captured, and was conspicuous from arrival because of her ferocity. She killed the first and second male with which she was housed, although both were larger than herself. The third attempt to mate her was successful, the male being a young adult captured in March, 1919. Their progeny comprised twenty-five young with the unusual sex ratio of three males and twenty-two females. All of these offspring were reared, with the exception of one female which died when about 2 weeks old, and all were normal grays. Eleven females in these litters were housed with their three brothers for several months, but no young were obtained. Ten females were mated with excess males from litters of the third pair of wild rats. As inbreeding the other offspring of wild female 3 and her mate gave fifty-eight normal gray young, this pair of wild rats did not carry genes for any of the recessive color mutations that later appeared in the strain.

Rats of the second generation were far better adjusted to conditions of captivity than were their parents. Individuals of one litter could be housed with those from other parents, with few casualties resulting. From this time until the twenty-first generation, few matings were made between rats that were very closely related. The young obtained by mating female offspring of the first pair of wild rats with males from litters of the third pair were so noticeably larger and more vigorous than other rats in the F_2 generation, that many of them were reared and crossed with progeny from other wild rats. Selection of the best litters in each generation to propagate the race tended to preserve the descendants of female 1 and her mate, and at the ninth generation they comprised nearly 88 per cent of all individuals in the strain. On tracing the pedigrees of the various mutant types that appeared, it was found that in each case the line of descent went back, unbroken on the maternal side, to the first pair of wild rats. Our present concept of the mechanism of inheritance does not permit of an assumption that this pair of apparently normal gray rats could have carried genes for all the recessive color mutations found. The dominant curly gene would have manifested its presence in the F_1 generation if it had been carried either by female 1 or by her mate. Considering the fact that, aside from the hooded rats, captive grays bred true to type until the eleventh generation, I am of the opinion that these various mutations had their origin in gene changes that occurred after the strain had been in captivity for several years.

Recent work in genetics has shown that gene mutations can be induced by x-rays, radium and other media, but as yet the agencies are unknown that cause such mutations in animals living under natural conditions, or in those maintained in laboratories under fairly uniform conditions of environment and nutrition. The suggestion, advanced years ago, that age changes in the variability of the germplasm may have an important role in the production of such mutations did not receive much support until Little ('33) cited various series of data indicating that there is an age-variability relation not only in the reactions of somatic tissues, but in the germ cells as well. Thus young and old mice exhibit an increased tolerance of tumor transplants as compared with that of young adults (Little, '20; Strong, '22). Variability in the litter size of inbred mice, as shown by coefficients of variation, changes with the age of the mother, being very high among the early litters cast, decreasing to a base level and subsequently rising in litters produced toward the end of the reproductive period.

In full accord with these findings for mice is the series of coefficients for litter size in captive gray rats, as given in table 10 of the present paper. Little ('33) states, "on a priori grounds there is no reason why the germ cells, as an organization, should not also show a durational phase in its various activities." In this connection Bridges ('29) has given data indicating that in Drosophila crossing-over varies with the age of the mother, the greatest variation being shown by very young and by very old females. Haldane and Crew ('25) found that in poultry linkage between two dominant sex-linked factors in males decreased steadily and had practically disappeared by the third year. This finding, they say, "is of interest as pointing to pre-senile changes in the behavior of the dividing nucleus, and as being the clearest case so far recorded in vertebrates of a change with age of the 'germ-plasm' of an individual."

That very young and very old germ cells may function more variably than do those of the middle age period seems further substantiated by the fact that in man some types of defects, which seemingly have an hereditary basis, are found more commonly among children of young mothers, while other types appear more frequently among the late-born. Pearson's ('14) analysis of a large series of data relative to the relation of the order of birth to various defects showed that congenital cataract, albinism, mental defects, tuberculosis and criminality have a particular tendency to occur among the first or second children. On the other hand, Mongolism shows a disproportionate frequency among the late-born, particularly in large families, as many investigators besides Pearson have shown (Langdon-Down, '06; Davenport and Allen, '25; Van der Scheer, '27; Penrose, '32, '33; Murphy, '36, etc.).

In the further development of his thesis Little ('33) also states:

> It might well develop that tendency to mutation, which in itself is an indication of variability, would be greater in very young and in very old germ cells. If this were true, domestication, in which very young and very old animals, protected

from the competitive factor of natural selection, are used as parents, would provide a far greater chance for mutations to occur than would natural conditions.

In this hypothesis may lie the explanation for the appearance of various mutations in captive gray rats after they had been under domestication for several years.

In early generations the breeding of gray rats was restricted mainly to the middle and most active period of reproductive life, therefore germ cells in young and old individuals had little chance to function. Females of the first nine generations did not cast their first litters until they were, on the average, over 7 months of age, and reproductive life averaged less than 8 months. In the period when mutations appeared breeding began at an earlier age and was continued much longer than in earlier generations (table 7). Three of the mutant types obtained, black, albinism, and ruby-eyed dilute, first appeared in litters cast by females that were from 14 to 16 months old, and so near the end of reproductive life. The first curly mutant was born when the mother was about 6 months of age. These findings, although forming but a very small series, are in accord with Little's hypothesis. Other investigations along this line may further confirm it. It may be true that "mutations are accidents and accidents will happen" (Sturtevant, '37), but to ascertain the basic cause of such 'accidents' still remains a major problem of genetics.

A general discussion of the effects of captivity on gray Norway rats is deferred until the final report, which will be given when data for the fiftieth generation have been obtained.

SUMMARY

The following summary of life processes in gray Norway rats during fourteen years of captivity covers the findings through the twenty-fifth generation. The data analyzed comprise a total of 8685 litters containing 53,077 individuals.

In both sexes of gray rats rate and extent of body growth increased gradually as the generations advanced (tables 1 to 3, figs. 1 and 2). At the last generation growth acceleration during the adolescent period was nearly equal to that found in stock albino rats that have been under domestication for a long period of time.

The growth rate in females during the suckling period was more rapid than that in males, but at all subsequent age periods males grew more rapidly than females.

At the twenty-fifth generation adult rats of both sexes were, on the average, about 20 per cent heavier than individuals of the first generation (figs. 3 and 4).

Rats attaining an adult weight much above the average for all individuals of like sex in the same generation group appeared in increasing numbers as the generations advanced (table 4, fig. 5). The weight increase in these individuals is ascribed, tentatively, to genetic factors that activated growth mainly during adult life. Some of these large rats, especially males, showed a tendency to maim or kill smaller individuals of the same sex.

In both sexes of gray rats body-weight variability decreased as the generations advanced. In males of the last generation variability during early life was about one-half that in males of the first generation, and subsequently was still further reduced (table 5, fig. 6). In females of this generation body-weight variability was less than that in females of the first generation at all age periods, but the decrease was significant only for periods during adult life (table 6, fig. 6). This marked decline in variability is attributed mainly to the method of selecting breeding stock and to inbreeding.

There was no sex difference at birth in the body-weight variability of gray rats, but males were more variable than females during early life and less variable during adult life. As the increased variability in adult females was due, probably, to weight fluctuations resulting from pregnancy and lactation, it is concluded that, on the whole, body-weight variability in males was slightly greater than that in females.

At the twenty-fifth generation the average length of the reproductive period was nearly 8 months longer than the average for the first generation (table 7, fig. 8). This extension was caused by the earlier breeding of the rats and the continuation of their reproductive activities to a more advanced age (fig. 7). Possible explanation for this lengthening of reproductive life are discussed briefly.

Fertility of gray rats, as measured by litter production, increased steadily, reaching its maximum in the nineteenth generation where females produced an average of 10.18 litters as contrasted with an average of 3.50 litters produced by females of the first generation. A slight decline in litter production during later generations resulted from the unfavorable effects on reproduction of changes in the location of the colony (table 8, fig. 9).

Sterility and low fertility of females, ascribable to the effects of captivity, had disappeared by the tenth generation. Subsequently all females reared were fertile, except those in which the reproductive organs became diseased.

In litters of the second to the twenty-sixth generation the range in litter size was from one to fifteen with the mean at 6.1 (table 9, fig. 10). Average litter size in any generation did not differ materially from the mean for the entire series.

The age of the mothers had a marked effect on litter production, litter size and the variation in litter size. The number of litters cast increased until the females were 7 months old and then decreased steadily until the end of reproductive life (table 10). Average litter size reached its maximum (6.55) when mothers were 8 months old and then declined, reaching its lowest point in litters cast at the end of the series (fig. 11). Variation in litter size was slightly below the mean for litters cast by very young females, and significantly lower in litters produced when females were at the height of reproductive activity. When fertility began to wane, variation in litter size increased gradually and reached its maximum in litters cast near the end of reproductive life (table 10).

The sex ratio showed no definite trend as the generations advanced, and for the entire series was 97.3 ± 0.57 (table 11, fig. 12). This ratio is significantly lower than that (105.2 ± 2.00) found in a strain of albinos maintained under the same conditions of environment and nutrition as the gray rats. A similar disparity in the sex ratios of white and colored races of man is noted (table 12).

The sex ratio was not influenced by litter size (table 13).

Data given suggest, but give no definite proof, that there was a cyclic change in the sex ratio of the young as the age of the mother advanced (table 14, fig. 13).

Mortality at birth was low in all generations, and only 265 stillbirths were recorded for the entire strain. Mortality was low, also, during the first year of life, averaging 4.2 per cent for males and 3.4 per cent for females: 79.9 per cent males and 76.6 per cent females lived to the age of 20 months. The mortality rate among older rats decreased as the generations advanced, indicating that under conditions of captivity the life span in both sexes was lengthened (table 15). The chief causes of death were pneumonia, which was more prevalent among males, and tumors which occurred mainly in females.

At the twenty-fifth generation gray rats had lost the high nervous tension and fear of man displayed by individuals in early generations. Females then took excellent care of their young and would serve as foster mothers if certain precautions were taken. Two of the outstanding traits in rats of early generations still persisted: adults continued to show antipathy to strangers placed in their cage, and exceptionally large rats, particularly males, were yet prone to attack small individuals of the same sex. Gray rats of later generations could be rendered as tame as are stock albinos if they were handled frequently during early life. It was then possible to use these rats for any kind of experimental work.

Several mutations affecting the color or the structure of the hair appeared in this strain of gray rats. Gray hooded rats were developed by selective breeding among the descendants of one pair of wild rats in the foundation stock that carried the hooded gene (figs. 14 to 20). Black, albino and ruby-eyed dilute mutants appeared in the twelfth to the fourteenth generations. Curly, a dominant mutation previously unknown in rats, emerged in the seventeenth generation (figs. 21 to 26). Another new mutation, cinnamon, was found in the twenty-second generation.

Reasons are given for attributing all these mutations, except hooded, to gene changes that occurred after the rats had been in captivity for some years, and a tentative explanation for their appearance is offered.

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PLATES

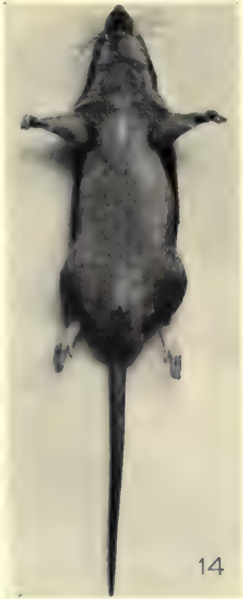
PLATE 1

EXPLANATION OF FIGURES

14 Ventral view of a rat showing location and size of the white area that indicated the presence of the hooded gene in female 2 of the foundation stock.

15 to 19 Stages in the development of the hooded pattern.

20 Coat pattern at final stage.



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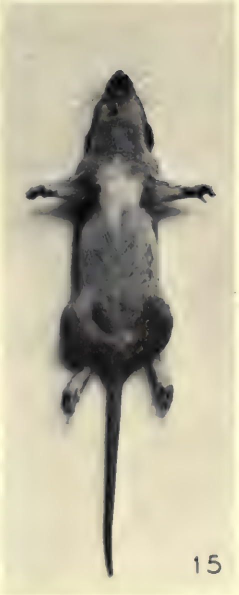

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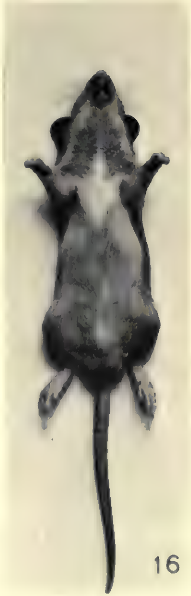

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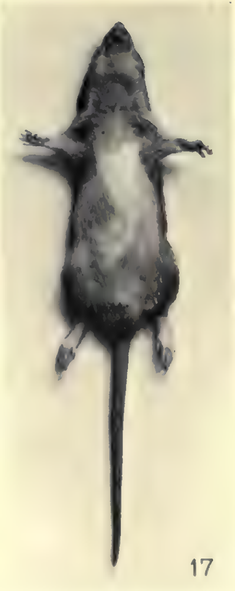

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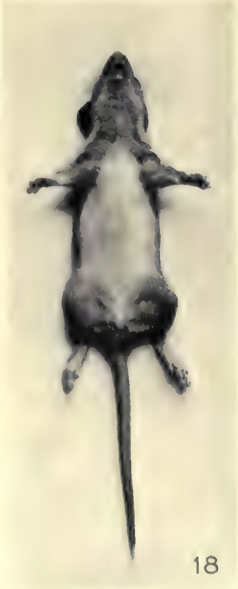

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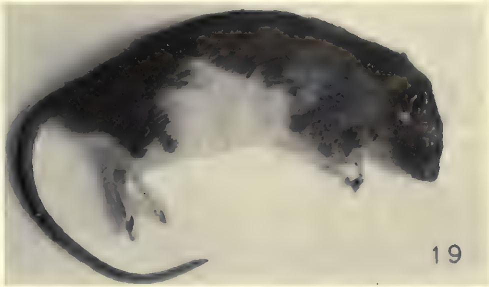

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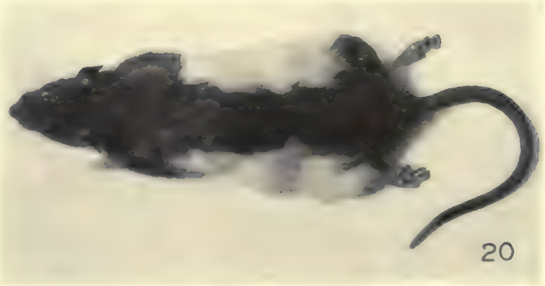

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PLATE 2

EXPLANATION OF FIGURES

21 Characteristic appearance of the coat in a curly mutant 16 days old.

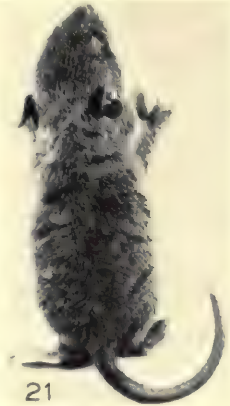
22 Enlargement of the head of rat in figure 21, showing modifications of the vibrissae.

23 Curly mutant 5 months old in which the curl has disappeared from the coat.

24 Curly mutant 8 months old. The curl is reappearing in the hair on the mid-dorsal surface.

25 Dorsal view of curly mutant 16 months old.

26 Ventral view of curly mutant 16 months old.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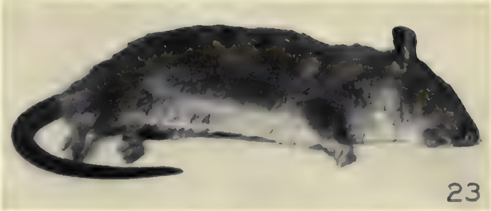
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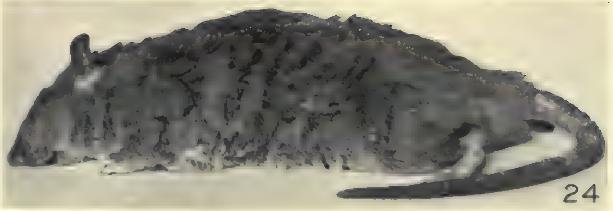
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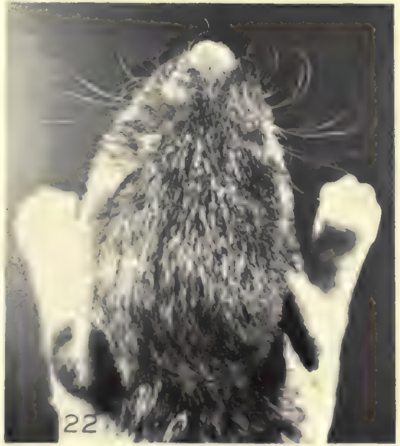
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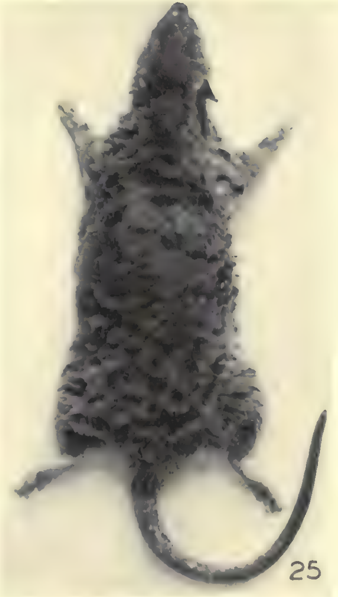
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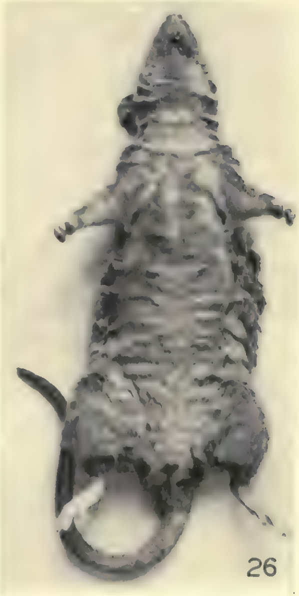
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